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HISTOPATHOLOGICAL ASSESSMENT OF PROGNOSIS OF IGA NEPHROPATHY

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CERTIFICATE

This is to certify that the dissertation titled **"HISTOPATHOLOGICAL ASSESSMENT OF PROGNOSIS OF IGA NEPHROPATHY"** submitted by **Dr.V.KANNAN BHABA** to the Faculty of Nephrology, The Tamilnadu Dr.MGR Medical University, Chennai in partial fulfillment of the requirement for the award of DM Degree in Nephrology branch is a bonafide work carried out by him under direct supervision and guidance.

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CONTENTS

Abstract:

Background of the study:

IgA nephropathy is the most common Glomerulonephritis in almost all parts of the world. It is unique among Glomerular diseases is being defined by immunohistochemical findings of Mesangial deposition of IgA. New OXFORD MEST scoring system introduced in 2010 uses four variables that predict the renal outcome accurately. These four variables are 1. Mesangial hypercellularity, 2. Endocapillary proliferation, 3. Segmental sclerosis and 4. Tubular atrophy.

Aim of the study:

To assess the Prognosis of IgA Nephropathy by NEW OXFORD MEST scoring system and to analyze other clinical, biochemical and histological factors in predicting the renal outcome.

Materials and Methods:

Renal case records of Department of Nephrology, Kilpauk Medical College from June 2008 to December 2010 were searched. Case records of Patients with renal biopsy finding of IgA nephropathy were included in this study.

NEW OXFORD MEST scoring system was applied and the severity of renal lesion at the time presentation was analyzed. The contribution of the Mean Arterial Pressure, baseline Serum Creatinine, Creatinine Clearance, Proteinuria, serum Uric Acid and serum Triglycerides in predicting the high Total MEST score was analyzed. Clinical,

Biochemical and Histopahtological factors other than MEST score in predicting the progression of the disease were also analyzed.

Results:

A total of 44 patients, 25 patients were males. Mean age group was 31 to 50 yrs of age (52.7%). Mean period of follow up was 17.2 months. Macroscopic hematuria was found in 11 patients (22%). Microscopic hematuria was found in all patients (100%). Systemic hypertension was found in all patients (100%). Nephrotic proteinuria was found in 12 patients (27.3%). Mean urine spot protein creatinine ratio of patients 2.61 gm per gm of creatinine. Mean serum creatinine of the patients was 2.06mg/dl. Mean creatinine clearance of Non Progressors and Progressors was 59.6ml/min and 28.63ml/min respectively. Mean total MEST score of Non Progressors and Progressors was 2.12 and 3.16 respectively. Disease progressed in 19 patients (43.1%) and more in males(58%). Disease progressed more in younger age group(15to30 yrs -63.15%).

Conclusion:

High Total MEST score at the time of presentation is an individual predictor of Disease Outcome. MEST score is neither superior nor inferior in predicting the Renal Outcome when compared to Creatinine Clearance and Nephrotic proteinuria.

Key words : IgA nephropathy, New Oxford MEST score.

Introduction :

IgA nephropathy is the most common Glomerulonephritis in almost all parts of the world where the renal biopsy is widely practiced[1a]. It is unique among Glomerular diseases is being defined by immunohistochemical findings of Mesangial deposition of IgA.

Diseases associated with glomerular IgA deposition can be divided into primary and secondary. Primary IgA nephropathy is an immune complex mediated glomerulonephritis. Diseases associated with primary causes are IgA nephropathy and Schonlein- Henoch Purpura.

IgA nephropathy is a renal limited disease, having a varied histological presentation. Histologically IgA nephropathy varies from Minimal lesion to diffuse proliferative glomerulonephritis.Focal mesangial proliferative glomerulonephritis is the most common presentation.

Schonlein- Henoch Purpura is distinguishable from primary IgA nephropathy by its dominant systemic manifestation in younger individuals. Dominant clinical features are Leukocytoclastic vasculitic lesion in lower limbs, abdominal pain, arthritis and renal involvement in the form of proteinuria and renal failure. Focal and diffuse glomerulonephritis with crescents are the dominant renal biopsy features.

Secondary causes of IgA deposits in mesangium are

1. Diseases of the liver: alcoholic, primary biliary, or cryptogenic cirrhosis; hepatitis B (where endemic);chronic schistosomiasis

2. Diseases of the intestine: Celiac disease; Chronic ulcerative colitis; Crohn's disease
3. Diseases of the skin: Dermatitis herpetiformis; Psoriasis
4. Diseases of the bronchus or lung: Sarcoidosis, Idiopathic pulmonary hemosiderosis; Cystic fibrosis;Bronchiolitis obliterans
5. Neoplasia: Carcinoma of the lung, larynx, and pancreas; Mycosis fungoides
6. Infection: Human immunodeficiency virus; Leprosy
7. Other systemic or immunologic disorders: Systemic Lupus Erythematosus; Rheumatoid arthritis; Cryoimmunoglobulinemia;
8. Psoriatic arthritis; Ankylosing spondylitis; Sjögren's syndrome; Behçet's syndrome;
9. Reiter's syndrome; Familial immune Thrombocytopenia; Autoantibody-mediated (monoclonalIgA–mediated) Goodpasture's syndrome
10. Diseases coincident with IgA nephropathy: AntiNeutrophilic Cytoplasmic Antibody–associated vasculitis;Diabetic nephropathy; Membranous Nephropathy; Granulomatous polyangitis

New Oxford MEST scoring system[60] is a newly emerging scoring system for IgA nephropathy that predicts the prognosis accurately. This scoring system consists of Mesangial hypercellularity, Endocapillary proliferation, Segmental sclerosis and Tubular atrophy.

Review of literature :

IgA nephropathy first became recognized as a distinct entity in 1968 by Berger and Hinglais from a cohort of patients with persistent Microscopic Hematuria, episodes of macroscopic Hematuria that were often associated with sore throat. Mild to moderate Proteinuria without Nephrotic syndrome and Normal renal function is the most common presentation[1]. Renal biopsies from these patients showed varying histological features ranging from normal to chronic glomerulonephritis, but most often focal glomerulonephritis, without typical features of acute post infectious glomerulonephritis. Immunoflourescence microscopy in each case showed mesangial deposition of IgA usually accompanied by less intense staining of IgG and C3. Electron microscopy confirmed the presence of mesangial immune complex deposits[2].

Incidence and prevalence of IgA nephropathy- world scenario:

IgA nephropathy is recognized as the most common form of primary glomerulonephritis in the world. Incidence and prevalence of IgA nephropathy in general population shows a considerable variation among geographical regions. The reported incidence in three regions in France and one each in the Netherlands, Germany and Italy varied from 15 to 40 new cases per million populations per year[3-7]. The incidence is higher in Japan, where routine screening for urinary abnormalities is performed in all school-agedchildren. 48 percent of Japanese children initially identified through urinary screening program who subsequently underwent a renal biopsy had IgA nephropathy[8].

Incidence of IgA nephropathy was, 45 new cases/100000 population in Japan, 43 per million populationin France , 10 per million population in USA , 6 per million populationNew Zealand (white) and 2 per million population in New Zealand(polynesian).

Prevalence appears highest in Asia (Singapore, Japan, andHong Kong).Prevalence in Australia, Finland, and southern Europeis reported to be 20 to 40 percent. In the United States prevalence rates of IgA Nephropathy was as low as 2 to 10 percent[9]. In Native Americans from New Mexico, the prevalence rate was 38 percent[9]. In a recent study of renal allografts in Japan revealed mesangial IgA deposition in 19 %(82 out of 510) and 19 of those had mesangial proliferation[10].

Incidence and prevalence- Indian scenario: - An increasing trend:

Available evidence suggests an increasing incidence in India. In 1987, a frequency of 4.2% was reported from Tamil Nadu[11]. In 1992, a frequency of 7.24% was reported from New Delhi[12] and in 1995, 10.37% was reported from the Union Territory of Chandigarh[13]. In retrospective study of IgA nephropathy from Kerala, out of 1592 renal biopsies, 227 cases were diagnosed as IgA nephropathy (14.26%). Of these, 85 out of 677 were in the first year (12.74%) and 142 out of 915 in the second year (15.52%) suggesting an increase in incidence[18].

Demography:

Primary IgA nephropathy occurs at any age, most commonly with clinical onset in the second and third decades of life[14].There is a Male: Female ratio ranging from less than 2:1 in Japan to as high as 6:1 in Northern Europe and the United States[15]. Whites and Asians are more prone to IgA nephropathy than are Blacks from the United States and from South Africa[16, 17].

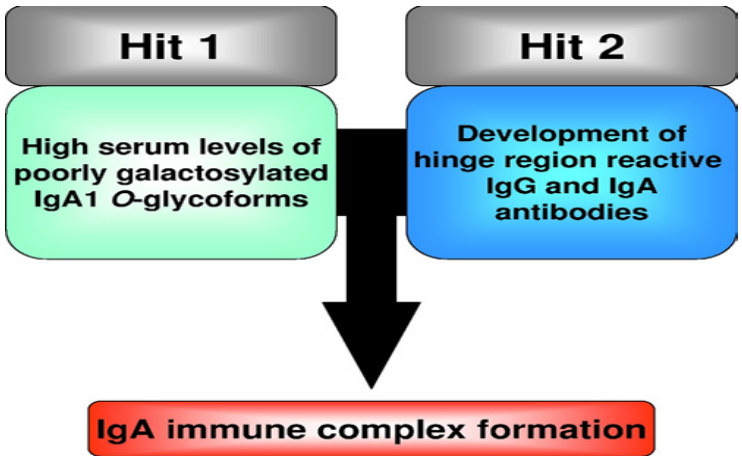
Pathogenesis:

The main hypothesis indicates that the development of the IgA nephropathy can be divided into three main stages: I) IgA deposit in the mesangium; II) generation of the mesangial lesion mediated by the interaction of the IgA1 complexes with specific receptors or through the activation of the complement, and III) progression of the mesangial IgA lesion towards chronic renal failure[19]. IgA Nephropathy is an immune complex glomerulonephritis that involves intense deposition of dimeric and polymeric forms of IgA1 within the mesangium of the glomerulus[24].

Stage 1: Deposition of IgA:

Fundamental to immune complex formation (IgA- IC formation) is excessive production of poorly O galactoylated IgA1 found in serum, however the presence of these excessive IgA1 *O* glycoforms alone is insufficient to cause IgA Nephropathy and a second hit is required for deposition in mesangium[20]. In this second hit, glycan specific IgG and IgA antibodies formed

and recognizes the poorly O galactosylated IgA 1 in the serum. Genetic factors heavily influence the level of poorly O galactosylated IgA1 in the serum and they alsoinfluence the autoantibody formation in IgAN[21-23].



The two-hit hypothesis for IgA-IC formation in IgAN

IgA molecule:

IgA molecule is a major immunoglobulin in mucosal secretions but is present in relatively low concentrations in serum. Its predominant function is in mucosal defense. Two subclasses of IgA exist in humans, IgA1 and IgA2, both of which occur in Monomeric (mIgA) and Polymeric (pIgA) forms. 90 % of Serum IgA is Monomeric whereas that found in mucosal secretion is Polymeric. IgA1 accounts for 90% of serum IgA, produced in bone marrow, lymph nodes, plasma cells and spleen. IgA2 comprises 60% in mucosal areas. Polymeric IgA contains the bridging or joining polypeptide – j chain- linked to the heavy chain during the formation of multimers within the plasma cell.

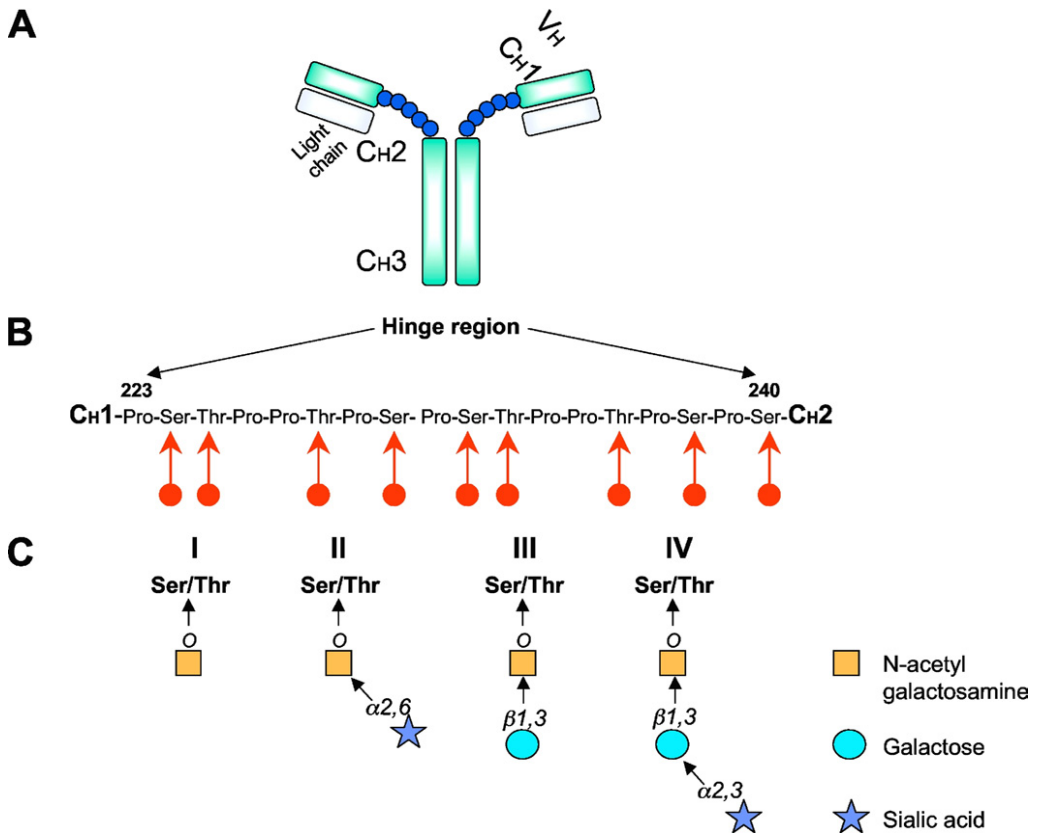
IgA1 possess an 18 amino acid in the hinge region between CH1 and CH2 domains of heavy chain. This is absent in IgA2 molecule. Hinge region consists of repeating sequence of proline, serine and threonine residues and carries multiple O linked carbohydrate side chains connected to serine and threonines. This O linked sugars of IgA1 molecule increase the size significantly and confers a high negative charge because of sialylation of sugars.

Galactosylation defect:

Under normal conditions, IgA1 molecules are glycosylated by the union of Nacetyl galactosamine (GalNAc) to the hinge region and forms Serine or Threonine/GalNAc complex, through the action of the beta-1,3 galactosyl transferase enzyme and forms the Gal-GalNAc disaccharide. And in this complex through the action of the alpha-2, 3 sialyltransferase enzyme, can incorporate one or two units of sialic acid[25, 26]. This is called sialylation.

IgA nephropathy patients present with glycosylation deficiency (hypoglycosylation) in hinge region. The immortalised B-cells of patients with IgA nephropathy produce galactosylation deficient IgA[27]. These cells present with reduced activity of beta-1, 3 galactosyl transferase and its chaperone (COSMC).But the Mutations in the genes of the beta-1, 3 galactosyl transferase (C1 GALT1) and COSMC are inconclusive. Premature sialylation of the IgA, as a consequence of an increase in the alpha-2,3sialyltransferase activity, could block the process of galactose incorporation. There is evidence that both the

alpha-2, 6 sialyl transferase as well as the expression of its ST6 GALNA C2 gene is altered in the IgA nephropathy[28-31]. These mutations prove that the glycosylation defect is hereditary[32].



The IgA1 molecule showing the position of the hinge region *O*-glycans and the major *O*-glycan forms found in human IgA1. (A) The hinge region of IgA1 lies between the CH1 and CH2 domains of the _1 heavy chain. The hinge region is made up of 17 amino acids. (B) Serineand threonine residues provide nine potential *O*-linked glycosylation sites (arrows); although to date only six are known to be occupied by *O*-glycans. It is still not known which amino acids are occupied by *O*-glycans and whether it is the same amino acids for all *O*-glycoforms of IgA1. (C) The IgA1 *O*-glycans are all based on a core 1 structure with GalNAc units in *O*-linkage with serine or threonine. This may occur alone (form I) or may be extended with either sialic acid in _2,6-linkage with GalNAc (form II) or _1,3-linked galactose (form III). Further extension with sialic acid in _2,3-linkage with galactose also can occur (form IV).

Aggregation of hypoglycosylated IgA;

The hypoglycosylated IgA1 has the capacity of self-aggregationand forms polymeric aggregates with other IgA1 molecules. The IgA1 polymers formed by self-aggregation, after interacting with the Fc alpha receptor on the surfaces of the lymphoid and mononuclear cells, can break its extracellular component and give rise to soluble polymeric IgA RR Fc alpha complexes that are deposited in the mesangium. The hypoglycosylated region of the hinge exposes immunogens that generate the production ofcirculating IgG antibodies, giving rise to immune complexes IgA1 polymeric-IgG. This macromolecular and immune complex persists in the circulation. They cannot be recognized by the hepatic Asialoglycoprotein receptors and are deposited in the renal mesangium due to their affinity to extracellular matrix proteins or through the interaction with specific mesangial receptors.

Polymeric IgA interaction with specific mesangial receptors

Transferrin TFR or CD71 receptor is expressed very little in quiescent mesangial cells, but it is found over expressed in IgA nephropathy patients[33]. CD71 is able to bind polymeric IgA1, but not monomeric IgA1, and several experimental data have shown that the polymeric IgA1-CD71 union causes an activation of the mesangial cell, which results in proliferation and production IL-6, TGF beta and other cytokines.

Activation of complement:

The polymeric IgA1 is able to activate the alternative route of the complement[34]. In some patients, polymeric IgA co-localizes with MBL and can activate the complement through the lectin route[35].

Stage II

Generation of mesangial lesion:

Mesangial cells preferentially bind to poorly O galactosylated IgA1 principally through the transferring receptor (CD71), triggers mesangial cell proliferation and apoptosis, reduced synthesis of vascular endothelial growth factor, altered integrin expression, and increased synthesis of extracellular matrix components[36].

Secretory component of IgA, with a high sialic acid content and its anionic property stimulates mesangial cells resulting in activation of the p42/p44 mitogen activated protein kinase, activator protein-1, and NF-Bsignal transduction pathways along with up-regulation of IL-6, transforming growth factor-β (TGF-β), tumor necrosis factor (TNF-α), monocyte chemoattractant protein1 (MCP-1), IL-8, and macrophage migration inhibitory Factor[37].

Podocyte injury:

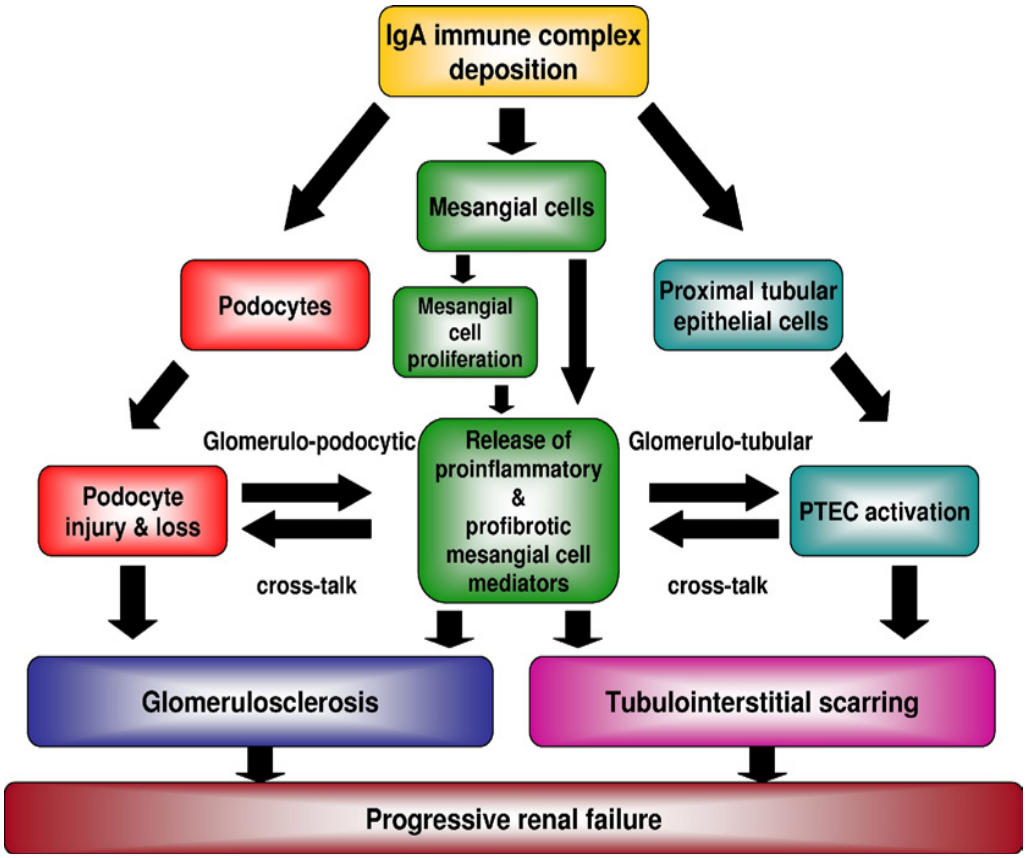
Necrosis and detachment of podocytes from the GBM has been reported in IgA Nephropathy and the degree of podocytopenia is closely related to the increasing severity of glomerular lesions[38].Nephrin mRNA and extracellular

nephrin expression are reduced in IgA Nephropathy, particularly in patients with heavy proteinuria[39]. Podocytes can bind IgA-IC but in a much lower affinity than mesangial cells. Podocytes do not express transferrin receptor but they may express another novel IgA Receptor and it is widely accepted that mesangial cells also express an undefined receptors for IgA[40]. Exposure to IgA-IC results in down-regulation of nephrin expression. Down-regulation of nephrin is likely to lead to structural and functional changes in podocytes manifest principally by foot process effacement and increased glomerular permeability.

Stage III. Progression of the mesangial IgA lesion towards chronic renal failure –tubulointerstitial scarring:

Until recently been thought that the mechanisms of subsequent tubulointerstitial injury were generic and common to all forms of chronic kidney disease. Recent work suggests that there may be direct and specific pathogenic interactions between filtered IgA-IC, mesangial cell– derived mediators, and proximal tubule epithelial cells (PTEC) [41]. PTEC are constantly exposed to filtered IgA-IC once the glomerular size barrier is impaired. PTEC can bind IgA with lower affinity than mesangial cells. There is some evidence that this binding is greater for IgA isolated from patients with IgAN[42].PTEC do express the transferrin receptor. There has been a single report of tubular expression of a novel polymeric immunoglobulin receptor, the Fcα/μ receptor[43].This receptor binds both IgA and IgM and appears to be expressed

exclusively by tubular epithelium, with no expression within glomeruli[43]. Mesangial cell– derived mediators have been shown to activate extracellular signal-regulated kinase and NF-_B signaling pathways, up-regulate IL-6,TNF-α, migration inhibitory factor, and intercellular adhesion molecule 1 expression, and alter expression of both the type 1 and type 2 angiotensin II receptors in PTEC[44]. Potential factors mediating this Glomerulo tubular cross-talk include angiotensin II, IL-1, IL-6, TNF-α, MCP-1, TGF-β, and platelet-derived growth factor. PTEC activation by mesangial cell– derived mediators appears to be influenced heavily by intracellular levels of the ligand-activated transcription factor PPAR-Ɣ[45].



Clinical features:

Pattern of clinical presentation:

Common:

1. Synpharyngitic macroscopic hematuria+/- loin pain
2. Microscopic hematuria
3. Hypertension
4. Chronic Kidney Disease
5. Henoch schonlein Purpura

Uncommon:

1. Malignant Hypertension
2. Acute Nephritic Syndrome
3. Acute renal failure
4. Nephrotic syndrome

Macroscopic Hematuria:

The most dramatic presentation is episodic macroscopic hematuria in young adults. Approximately 40 to 50 percent of the patient presented with macroscopic hematuria. Hematuria has a characteristic temporal association with upper respiratory tract infection. Hematuria usually coincides with or

occurring within 1 to2 days of the sore throat. Hematuria is usually painless but often associated with systemic symptoms such as fever, malaise, fatigue, diffuse muscle aches and dull loin pain. Macroscopic hematuria occurs more frequently in children and young adults than in middle or elderly patients. This feature is virtually never seen after the age of 40 yrs.

Asymptomatic Hematuria:

Approximately 30 to 50 percent of the IgA nephropathy patients are incidentally discovered by microscopic hematuria. This occurs at any age but it is typical in older patients. There is an iceberg effect in the prevalence of this presentation.

Proteinuria and Nephrotic syndrome:

Proteinuria in the absence of hematuria is an uncommon presentation. Nephrotic range proteinuria is also uncommon, but can occur in the presence of very active disease or advanced disease with considerable scarring. The presentation is only 5 percent of all IgA nehropathy.

Hypertension and Malignant hypertension:

An important proportion of patients with IgA nephropathy are detected during investigation of newly diagnosed hypertension. It is one of the major causes of hypertension in young adults. Malignant Hypertension is the one of the most dramatic presentation in IgA nephropathy.

Acute renal Failure:

ARF is an uncommon feature in de novo IgA nephropathy, occurring in only 5 percent of the patient. It may occur during episodes of Macroscopic Hematuria, possibly as a result of tubular obstruction by red blood cells.

Rapidly progressive renal failure:

This usually occurs as a result of acute necrotizing, Crescentic glomerular injury. It is a strongest indicator of aggressive immunosuppressive therapy. It is an analogous to pauci immune crescentic glomerulonephrits[46]. There are number of cases that seem to be associated with IgA ANCA, but overall findings are inconsistent. A few patients had linear capillary wall IgA deposition, presumably an IgA variant of Good Pasture syndrome[47].

Chronic Renal Failure;

Approximately 10 to 20 percent of patients with IgA nephropathy had chronic established renal failure at presentation. This fact is clouded by late attention in the course of renal disease; since many do not have a renal biopsy. Undoubtedly many of those with end stage or near end stage renal disease with small kidneys had unrecognized IgA nephropathy for years or decades. The lack of a reliable peripheral diagnostic marker of IgA nephropathy is an obvious deficit.

Histopathological features and classification of IgA nephropathy:

The first histological lesions that appear in the glomeruli are increased extra cellular matrix and hypercellularity of the mesangium. Subsequently, the spectrum of glomerular abnormalities may enlarge and virtually all morphological manifestations of glomerular abnormalities such as floculo capsular adhesions, segmental sclerosis and crescents may be observed. For this reason different classification systems have been introduced.

Earlier classification system:

Lee SM et al[48] in 1982 evaluated the clinical and pathologic findings of 20 unselected patients with IgA nephropathy. 13 patients were followed for 1.5 to 5 years (mean 2.8 years).The activity and severity of the lesions were graded according to a modified classification used by Meadow et al. for the nephropathy associated with Henoch-Schönlein Purpura[49]. The results reveal a correlation between the histopathologic grading in the initial biopsy and the clinical outcome: Patients with mild (grade II) or moderate (grade III) lesions had a benign course or showed evidence of active disease without deterioration of renal function, whereas all patients with grade IV or V lesions who were followed for more than one year developed end-stage renal failure. These observations suggest that histologic grading at initial renal biopsy may be a useful prognostic indicator of the clinical outcome of IgA nephropathy.

Histological Classification of IgA Nephropathy of LEE et al		
Histological Grade	**Glomerular changes**	**Tubular and Interstitial changes**
I	Mostly normal occasional slight mesangial thickening with or without hypercellularity	Absent
II	Less than 50% of glomeruli show localized mesangial proliferation and sclerosis, rarely small crescents	Absent
III	Diffuse mesangial proliferation with focal and segmental variation occasional small crescents	Focal interstitial edema and infiltrate ,tubular atrophy rare
IV	Marked diffuse mesangial proliferation and sclerosis, crescents <45% of glomeruli	Tubular atrophy, interstitial inflammation and occasional interstitial foam cells
V	Similar to IV but more severe crescents in > 45% of glomeruli	Similar to IV but more severe
Lee SM, Rao VM, Franklin WA, Schiffer MS, Aronson AJ, Spargo BH, Katz AI: IgA nephropathy: Morphologic predictors of progressive renal disease. *Hum Pathol*13: 314–322, 1982		

Mark Hass et al in 1997 published the histologic features of 244 cases of IgAN (not including Schlinlein-Henoch nephritis) diagnosed between 1980 and 1994 and was subclassified using the following, relatively simple histologic classification schema[50]:

Histologic Subclasses of IgA Nephropathy: Definitions

Subclass I
Minimal histologic lesion
The glomeruli show no more than a minimal increase in mesangial cellularity, without segmental sclerosis or crescents.

Subclass II
Focal-segmental glomerulosclerosis-like
The glomeruli show focal and segmental sclerosis in a pattern resembling primary focal-segmental glomerulosclerosis, with at most a minimal increase in mesangial cellularity, and no crescents

Subclass III
Focal proliferative GN
Fifty percent or fewer of the glomeruli are hypercellular. The increase in cellularity may be limited to mesangial areas, or there may be obstruction of glomerular capillaries by proliferated endocapillary cells. Crescents may be present. While the great majority of subclass Ill lesions show segmental glomerular hypercellularity, this is not a requisite for assigning a biopsy specimen to this subclass

Subclass IV
Diffuse proliferative GN
More than 50% of the glomeruli are hypercellular. As with subclass Ill, the hypercellularity may be segmental or global, and crescents may be present.

Subclass V
Advanced chronic GN
Forty percent or more of the glomeruli are globally sclerotic, and/or there is 240% tubular atrophy or loss in the cortex as estimated from periodic acid-Schiff-stained sections, If these features are present, the biopsy specimen is assigned to subclass V regardless of other histologic features.

Hass et al borrowed the features from Lee et al, WHO Lupus Nephritis classifications and from D'Amico et al[51] with respect to multiple individual renal survival in a large cohort of Italian IgA nephropathy patients.

Mark Hass et al[50], find the statistically significant correlation between histologic subclass and renal survival, with an order I, II (greatest survival) > Ill> IV, V. Crescents were a significant negative prognostic indicator for renal survival in subclass Ill (but not in subclass IV), and interstitial expansion was a negative prognostic indicator in subclasses Ill and IV, although the statistical significance of these were not maintained after controlling for serum creatinine at the time of biopsy. The presence of peripheral glomerular capillary deposits ultrastructurally had no prognostic significance. With respect to clinical presentation, hypertension and proteinuria of >2.0 g/24 hour were significant negative prognostic indicators for renal survival, even when controlling for serum creatinine at the time of renal biopsy. The presence of gross hematuria correlated significantly with increased renal survival by univariate analysis, but was not correlated when controlled for serum creatinine at the time of renal biopsy. The findings of this study confirm the wide variety of clinical and histopathologic presentations of IgAN, and indicate the utility of the proposed histologic classification schema in assessing a patient's likelihood of ultimately developing end-stage renal disease.

These earlier classification systems divide the group into Lumped and Split. Lumped system was introduced by Lee et al[48] and mina and Murphy et

al[52]. Split system was used by Kobayashi et al[53] (1983), Andreoli and Bergstein et al[54] (1989),Alamartime et al[55] (1990) and Waldo et al [56] (1993). Lumped system is used for its simplicity and easy application in large multicentre studies. This scoring system as mild, moderate and severe is valuable in the analysis of a large clinical database. The weakness of the lumped system is the lack of flexibility in interpretation and important pathological changes are missed. The lumped system is more useful for diagnosis and grading of IgA nephropathy. The Split system gives the detailed analysis of each lesion by introducing a global score which provides the information on glomeruli, tubules, interstitium and vessels. This system has more flexibility and minimal intercentre variability. The Split system gives more information regarding the progression of the disease.

Classification system by Chrug and Sobin[57] (1982) was accepted by World Health Organisation and recently updated[58] (1995) and revised (2000). This scoring system was slightly modified from Pirani and Salinas –Marrigal[59] classification (1968).This grading system is based on the severity of cellular proliferation and glomerulosclerosis, number of crescents and presence and absence of tubular atrophy and interstitial cellular infiltration or fibrosis. This classification system divides the lesion into three grades: G1 mild includes patients with minor or minimal lesions, G2 moderate includes patients with focal-segmental or diffuse proliferative glomerulonephrits, G3 severe includes

patients with sclerotic lesions in advance chronic glomerulonephritis or end stage renal disease.

Histological classification of IgA nephropathy, Chrug and Sobin. Accepted by WHO(1995)			
Grade	**class**	**Glomerular changes**	**Tubulo interstitial changes**
I	A	Normal glomeruli	
	B	Slight mesangial hypercellularity	
	C	Slight mesangial matrix expansion	
II	A	<25% of the glomeruli with moderate focal and segmental mesangial proliferation and rare sclerosis. Rare crescents	Occasional focal interstitial infiltrate
	B	Up to 50% of the glomeruli with moderate focal and segmental mesangial proliferation and sclerosis. Capillary obstruction by endocapillary cell proliferation. Adhesions and cellular crescents less than 25% of glomeruli	Focal infiltrate less than 25% of cortical area
	C	>50% of the glomeruli with segmental proliferation and sclerosis. Adhesions and cellular crescents up to 50% of glomeruli	Tubular atrophy and interstitial infiltrate up to 50% of the cortical area.
III	A	<25% of the glomeruli with focal and segmental or global sclerosis. Adhesions and fibrous crescents less than 25% of glomeruli.	Tubular atrophy, interstitial infiltrate and sclerosis in less than 25% of the cortical area.
	B	Sclerosis up to 50% of glomeruli. Adhesions and fibrous crescents up to 50%of glomeruli.	Tubular atrophy, interstitial infiltrate and sclerosis up to 50% of the cortical area
	C	Sclerosis more than 50% of glomeruli. Adhesions and fibrous crescents in more than 50% of the glomeruli	Tubular atrophy. Interstitial infiltrate and sclerosis more than 50% of the cortical area.

New oxford MEST scoring system:

A Working Group of the International IgA Nephropathy Network and the Renal Pathology Society headed by Daniel C. Cattran, Rosanna Coppo, H. Terence Cook, Ian S.D. Roberts, John Feehally introduced this new scoring system[60].The Goal of this new system was to identify specific pathological features that more accurately predict risk of progression of renal disease in IgA nephropathy. In this retrospective analysis sequential clinical data were obtained on 265 adults and children with IgA nephropathy who were followed for a median of 5 years. Renal biopsies from all patients were scored by pathologists blinded to the clinical data. Four variables: (1) the mesangial hypercellularity, (2) segmental glomerulosclerosis, (3) endocapillary hypercellularity, and (4) tubular atrophy/interstitial fibrosis were analyzed for their independency in predicting renal outcome. The value of crescents was not addressed due to their low prevalence in the enrolled cohort.

Recommended elements in renal biopsy repot for a case of IgA nephropathy:

Detailed description of the features present on

Light microscopy, immunohistochemistry, Electron microscopy

Summary of Four key pathological features

Mesangial score <0.5(M0) or >0.5(M1)

Segmental sclerosis absent (S0) or present (s1)

Endocapillary hypercelluarity absent (E0) or present (E1)

Tubular atrophy/Interstitial fibrosis <25 %(T0), 25-50 %(T1) or >50%(T2)

Total number of glomeruli with endocapillary hypercellularity, extracapillary hypercellularity, global glomerulosclerosis,and segmental glomerulosclerosis

Definitions of pathological variables used in the New oxford MEST classification of IgA nephropathy		
Variable	**Definition**	**Score**
Mesangial Hypercellularity	<4 mesangial cells/mesangial area=0 4-5 mesangial cells/mesangial area=1 6-7 mesangial area/mesangial area=2 >8mesangial area/mesangial area=3	Mo <0.5 M1 >0.5
Mesangialhypercellulrity score is the mean score for all glomeruli		
Segmental glomerulosclerosis	Any amount of the tuft involved in sclerosis, but not involving the whole tuft or the presence of an adhesion	S0-absent S1 –present
Endocapillary hypercellularity	Hypercellularity due to increased number of cells within glomerular capillary lumina causing narrowing of the lumina	E0- absent E1 – present
Tubular atrophy/ Interstitial fibrosis	Percentage of cortical area involved by the tubular atrophy or interstitial fibrosis, whichever is greater	0 -25% -T0 26-50% -T1 > 50% –T2

Reproducibility of pathology variables:

A Working Group of the International IgA Nephropathy Network and the Renal Pathology Society headed by Ian S.D. Roberts validated the Reproducibility of pathology variables[61].

Along with the scoring systems using the four variables, mesangial hypercellularity, segmental glomerulosclerosis, endocapillary proliferation and Percentage of Tubular atrophy/Interstitial Fibrosis, additionally the cellular/ fibro cellular crescents and arteriolar lesion are also scored.

Extra capillary scoring was done by multiplication factor of 1 was applied for lesions <10% of the glomerular circumference, factor of 2 for lesions 10–25% of the glomerular circumference, factor of 3 for lesions 26–50% of the glomerular circumference, and factor of 4 for lesions 45% of the glomerular circumference. The resulting scores were summed and divided by the total number of glomeruli in the biopsy.

For most histological variables, the median score was taken for analysis. Reproducibility was assessed statistically using Intraclass correlation coefficients(ICCs). On the basis of the ICC scores, lesions were divided into three groups as follows

Group 1: Those lesions showing good or very good reproducibility (>0.6) were mesangial cellularity score, percentage of global glomerulosclerosis, percentage of cellular fibrocellular crescents, cellular/ fibrocellular crescent score (including adjustment for size of crescent),tubular

atrophy, interstitial fibrosis, interstitial inflammation1, and arterial scores 1, 2, and 3.

Group 2: Those lesions showing moderate reproducibility (0.4–0.6) were extent of segmental glomerulosclerosis and percentage of glomeruli showing either segmental or globalendocapillary hypercellularity.

Group 3: Those lesions showing poor or fair reproducibility (<0.4) were percentage of normal glomeruli, presence of adhesions, percentage of glomeruli showing segmental endocapillary hypercellularity, presence of glomerular basement membrane duplication, presence of necrosis, percentage of glomeruli showing fibrous crescents, interstitial inflammation (inflammation involving non-fibrotic cortex), and arteriolar hyalinosis.

The pathological variables that continued to show poor reproducibility (group 3) within the working group were not incorporated into final classification.

Finally the following six pathological variables showed good reproducibility in subsequent analysis, 1.Mesangial hypercellularity score: percentage of glomeruli showing, 2.segmental glomerulosclerosis, 3.endocapillary proliferation, 4. Cellular / fibro celluar crescents, 5. Percentage of Tubular atrophy/Interstitial Fibrosis and 6. Arterrosclerosis score, was taken for extended pathology dataset.

Validation of Oxford Classification of IgA nephropathy:

Andrew M. Herzenberg, Agnes B. Fogo, Division of Nephrology, Toronto General Hospital, University of Toronto, Ontario, Canada, validated

the Oxford classification of IgA nephropathy using an independent cohort of 187 adults and children with IgA Nephropathy from 4 centers in North America[62]. The cohorts had similar clinical and histological findings, presentations, and clinicopathological correlations with Oxford cohort. Three of the four pathological variables identified in the Oxford derivation cohort predicted a rapid rate of renal-function decline in the NA validation data set, supporting the original findings. In comparison with the Oxford cohort, an interaction between the E-score and the use of immunosuppressive therapy and the rate of renal-function decline was validated. This illustrates the potential role of renal biopsy findings in the selection of IgA patients requiring aggressive therapy. During follow-up, however, the North American cohort received more immunosuppressive and anti hypertensive therapies than oxford cohort.

Natural history of IgA nephropathy:

There is a marked variability in clinical outcome of primary IgA nephropathy, with a spectrum ranging from complete disappearance of blood and protein in the urine to the development of chronic renal failure. Microhematuria disappears spontaneously in 3 to 25 % of the patients. The overall clinical outcome shows that 60-80 percent of patients continue to have normal renal function for a mean follow up 2 – 5 yrs[63]. Renal biopsies from these patients usually reveal no change or only minimal glomerular lesion.

Stable renal function is generally present in mild form of mesangial proliferation. Patients with normal or stable renal function have mild proteinuria, normal blood pressure, and mild histological lesion. A small proportion patient with macro hematuria, loin pain and normal serum creatinine rapidly progress to end stage renal disease in 2 to 3 yrs. In these cases the renal lesions are characterized by crescents and progressive loss of renal structure in glomeruli.

Patients with Cresentic IgA nephropathy have an increased prevalence of hypertension, renal insufficiency and nephrotic range proteinuria. Patients with proteinuria of more than 3.5 gm /day and impaired renal function develop chronic renal insufficiency within a short period of appearance of clinical symptoms. A few patients have a very rapid course and terminates in renal failure are referred as malignant IgA nephropathy.

Prevalence of chronic renal insufficiency appears to be greater in Australian (23 %) and European (23 %) than in patients from Asia (13 %) and North America (15 %). The renal impairment is more common in males. Hogg et al[64] (1994) found observed 15 percent of the patients developed end stage renal disease for a mean follow up period of 4 yrs. Seven variables were found predictive of end stage renal disease, 1.presence of glomerular sclerotic changes in more than 20 percent of glomeruli, 2. Afro American race, 3 .Male gender, 4.Hypertension at biopsy, 5. Proteinuria at biopsy 6.older age at presentation and 6. Presence of crescents in renal biopsy.

Aim of the study:

1. To assess the Prognosis of IgA Nephropathy by NEW OXFORD MEST scoring system.

2. To assess the role of Clinical, Biochemical and Histo pathological parameters other than MEST score (Crescents, Arteriolar Hyaline, and Blood Vessel Thickening) in predicting the Renal Outcome.

3. To assess the correlation of baseline Mean Arterial Pressure, Serum Creatinine, Glomerular Filtration Rate and Proteinuria with MEST score

4. To assess whether the MEST score is superior in predicting the Renal Outcome when compared to baseline Mean Arterial Pressure, Serum Creatinine, Creatinine Clearance and Proteinuria.

Materials and study protocols:

This is a Retrospective cohort study, done at Kilpauk Medical College Nephrology department. This study protocol was approved by the Ethical committee for research studies of Government Kilpauk Medical College Hospital, Chennai.

Renal case records of Department of Nephrology, Kilpauk Medical College from June 2008 to December 2010 were searched. Case records of Patients with renal biopsy finding of IgA nephropathy were included in this study.

Renal case records were thoroughly searched for *clinical presentation (*age, SHT, Diabetes mellitus, fever with throat pain, macroscopic hematuria, pedal edema, oliguria, loin pain, blood pressure and anthropometric measurements), *urinalysis* (urine protein, RBC's and RBC cast in urine, urine spot protein creatinine ratio (PCR), and urine culture and sensitivity, *blood biochemistry* (blood sugar, urea, serum creatinine, serum sodium, serum potassium , serum uric acid, total proteins, albumin, globulin and serum lipid profile) *histopathological report of renal biopsy* (both light microscopy and immunofluorescence microscopy results) and *follow up investigations and treatment modalities*.

Creatinine clearance was calculated with Cockgrauft Gault Formula. The patients were divided into groups according to the serum creatinine at the

time of presentation. The group of patients according to serum creatinine were; group I <1.0mg/dl, group II 1.1 to 1.5 mg/dl and group III >1.6 mg/dl.

By applying the NEW OXFORD MEST scoring to each group (group divided according to the serum creatinine level) separately the severity of renal lesion at the time presentation was analyzed. MEST scoring system consists of Mesangial hypercelluarity, Endocapillary proliferation, Segmental sclerosis and Tubular atrophy. The contribution of the Mean Arterial Pressure, baseline Serum Creatinine, Creatinine Clearance, Proteinuria, serum Uric Acid and serum Triglycerides in predicting the high Total MEST score (score of 3 and above) was analyzed. Clinical, Biochemical and Histopahtological factors other than MEST score in predicting the progression of the disease were alsoanalyzed.

Follow up Serum creatinine, urine RBC and urine spot Protein Creatinine Ratiowas done to assess the latest renal status.

Total patients were divided into two groups; ie Progressors and Non Progressors. Progressors were defined as those who had doubling of serum creatinine, development of ESRD or initiation of Renal Replacement Therapy. Non Progressors had stable serum creatinine or had improvement in serum creatinine during the followup period.

Apart from clinical, biochemical ,MEST score and immunofluorescence findings, the associated renal biopsy findings including Cellular or Fibro cellular crescents, Arteriolar hyaline, Blood vessel thickening, Mesangiolysis,

Glomerular basement thickening and Capillary loop IgA deposit were also analyzed. Intensity of IgA deposits and co deposits like IgG, IgM, C3 and C1q in renal tissue was analyzed for its contribution in progression of disease.

Statistical analysis was done to identify significance and correlation of total MEST score, clinical, biochemical and other histopathological variables in predicting the renal outcome. Statistical analysis was done using SSPS 15 software. Univariate analysis was done with paired t test and Pearson product moment correlation coefficient. Multivariate analysis was done with logistic regression, Cox regression and Kaplan Meier survival analysis.

245 renal biopsies were done between June 2008 and December 2010. 48 patients with biopsy proven IgA nephropathy were enrolled in the study. Among the 48 patients, 44 patients were followed in our hospital regularly or irregularly, Rest of the 4 patients lost follow up. We excluded these 4 patients from our study because of incomplete case records.

Summary of Observation and Results :

Univariate analysis : 'paired t' test

Data	Non progressor	Progressor	P value
Total no of patients	25	19	
Mean Age	37.12yrs	32.16 yrs	
Predominant Age group	31 -50 yrs	15-30 yrs	
Disease status	56.9%(M>F)	43.1%(M (58%)>F)	
MAP	109±37 mm Hg	110±51mmHg	P=<0.05 NS
Nephrotic Proteinuria	16%	42.1%	
Macroscopic Hematuria	28%	21%	
Oliguria	64%	73.6%	
Microscopic Hematuria	100%	100%	
BMI	23±3.67 kg/m^2	21.19±3.20 kg/m^2	P=>0.05 NS
Urine PCR	2.16±1.13	6.06±1.59	P=0.01
Serum Creatinine	1.4mg/dl	2.70mg/dl	P=>0.05 NS
Serum Uric acid	5.8±1.65 mg/dl	7.5±1.69 mg/dl	P=0.005
Serum TGL	176.24±48.68mg/dl	179.42±34.29mg/dl	P=>0.05 NS

Data	Non progressor	Progressor	P value
Creatinine Clearance	59.60±27.86 ml/min	29.29±13.60ml/min	P=0.005
Total MEST	2.12±1.01	3.16± 0.76	P=0.005
MEST & Creatinine<1.0	1.43±0.79		Invalid
MEST&Creat 1.1 to 1.5	2.00± 0.93	2.50± 0.71	P=>0.05 NS
MEST&Creatinine>1.6	2.70± 0.95	3.24±0.75	P=>0.05 NS
IgA intensity	3.48±0.59	3.53±0.80	P=>0.05 NS
Co deposits	C3 predominant	C3 predominant	
Cellular crescents	20%	31.5%	
Severe BV thickening	8%	10.5%	
Arteriolar hyaline	Nil	Yes	

Summary of Pearson Product Moment Coefficient:

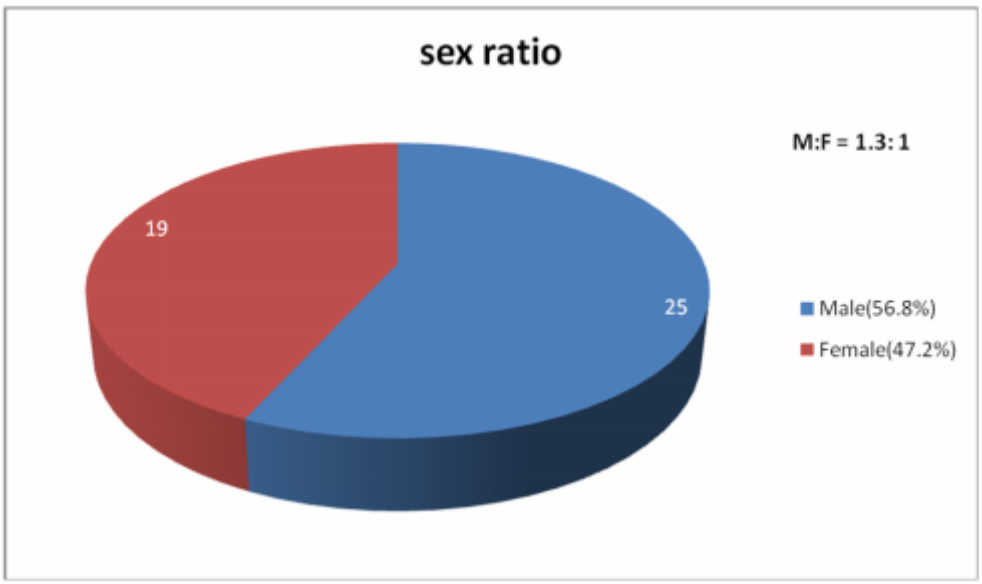
Data	Non progressor	Progressor
MAP VS MEST SCORE	p=<0.01 significant	P=>0.05 NS
TGL VS MEST SCORE	P=<0.01 significant	P=>0.05 NS
PCR VS MEST SCORE	P=>0.05 NS	P=<0.01 Significant
CR.CL VS MEST SCORE	P=<0.01 significant	P=<0.01 Significant
URIC ACID VS MEST SCORE	P=>0.05 NS	P=>0.0 NS

Summary of Multivariate Analysis:

Logistic regression analysis	Statistically not significant	
Cox regression analysis	Statistically not significant	
Kaplan Meyer survival analysis	Renal survival with reference to T score- significant	Renal survival with reference to crescents – significant

Observations and Results in detail :

245 Renal biopsies were done between June 2008 and December 2010. IgA nephropathy was found in 44 patients. Incidence of IgA nephropathy in our study was 16% (n=44). 25 patients were males (56.8%) and 19 patients were females (47.2%).Male: Female ratio was 1.3:1



Age distribution:

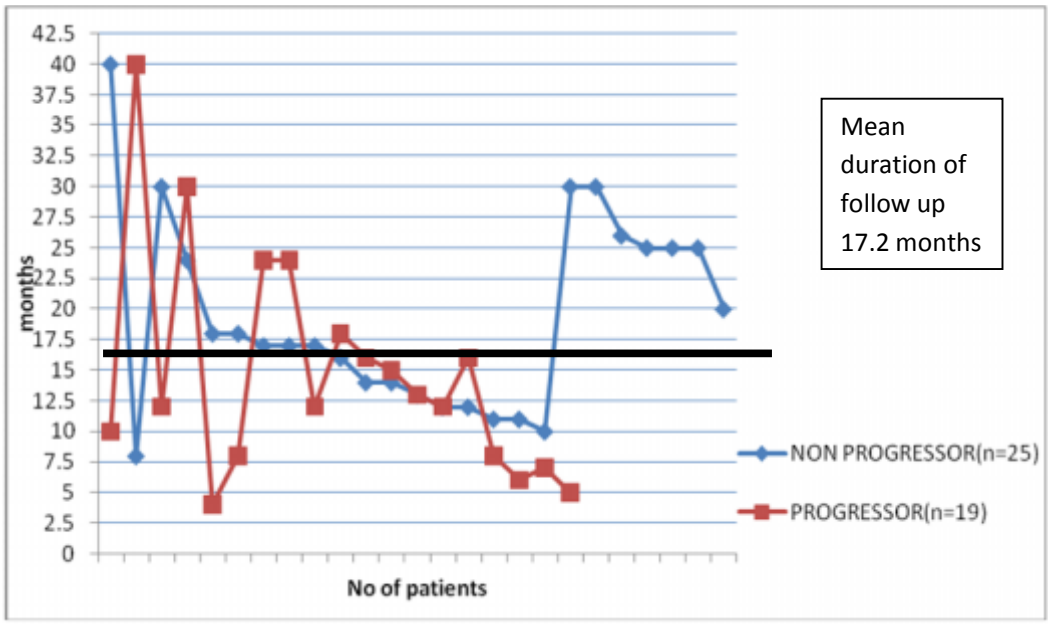
Age group	No of patients	Percentage
15 -30 yrs	20	45.45%
31 – 50 yrs	23	52.7%
51 – 65 yrs	1	2.27%

Dominant age group of our patient was between 31 to 50yrs (52.7%) (n=23). 20 patients were in the age group of 15 to 30 yrs, 23 patients were in 31

to 50 yrs age group and one patient was in 51 to 65 yrs age group. Mean age group of the patient was 35.2 yrs.

Duration of follow up (in months)

Mean period of follow up of the patients was 17.2 months. Follow up period varied from 4 months to 40 months. Non Progressors were followed for a mean period of 19.32 months, whereas Progressors were followed up for a mean period of 14.1 months. Time to Renal Replacement Therapy in Progressors was 5.2 months.



Clinical presentation:

Among 44 patients, 5 patients had past history of Hypertension (11.3%) and on treatment for a period of 2 to 9 yrs. Diabetes mellitus were found in 2 patients (4.5%). Duration of Diabetes Mellitus was 2 years in one patient and 6 years in another patient. Three patients had history of fever during initial

presentation (6.8%); none of the patients had throat pain. Except 2 patients all presented with pedal edema (n=42) (95.4%).

Age group	Progressor (43.1%)	Nonprogressor (56.8%)
15-30	12(63.15%)	8
31-50	6	17(68%)
51-65	1	0
Total no of patients	19	25

In 25 out of 44 patients (56.8%) the disease was stable, these patients were considered as Non Progressors. Predominant age group of Non Progressor was 31 to 50 years of age (68%). In this group, Systemic Hypertension and Diabetes Mellitus was found in one patient respectively.

The Disease progressed in 19 patients (43.1%). Progression of disease was defined as doubling of serum Creatinine, End Stage Renal Disease or initiation of Renal Replacement Therapy. In Progressors (n=19), past history of Systemic Hypertension was found in 4 patients and one patient had diabetes mellitus in addition to SHT. Disease progression was more in younger age group (15 to 30 years)(12 patients -63.15%) and in Male patients (58%).

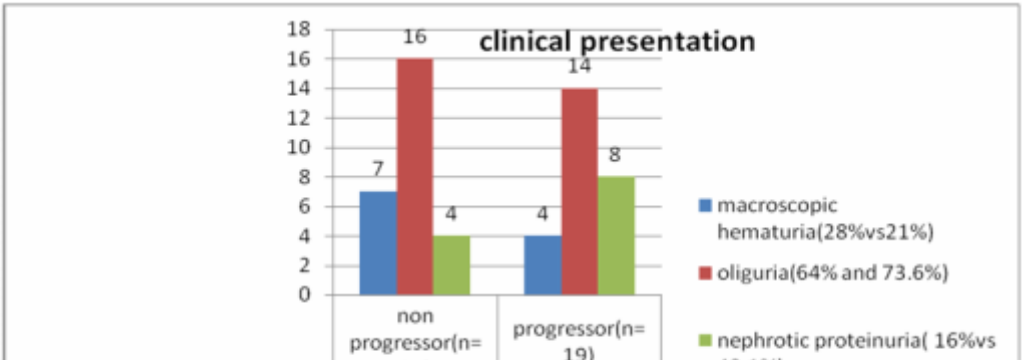
11 patients (22%) had macroscopic hematuria. Macroscopic hematuria was found in 7 (28%) and 4 patients (21%) of Non Progressors and Progressors respectively. Microscopic hematuria was found in all patients (100%).

4 patients (9.0%) presented with loin pain and 30 patients (68.1%) had Oliguria. Oliguria was a clinical feature in 16 (64%) and 14 patients (73.6%) of Non Progressors and Progressors group respectively.

Systemic hypertension was found in all patients at the time of presentation. The Mean Arterial Pressure of Non Progressors and Progressors were 109±37 mmHg and 110±51mm Hg respectively. Statistical correlation with Pearson product moment coefficient was not a significant predictor of disease progression with reference to mean arterial pressure (p=>0.05).

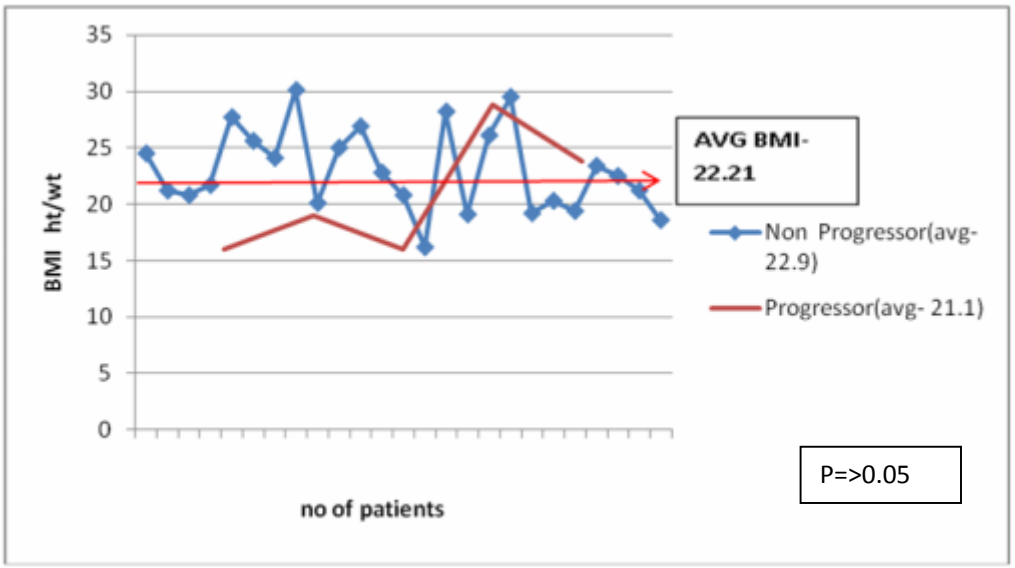
Nephrotic Proteinuria was present in 12 patients (27.3%). Nephrotic Proteinuria in Non Progressor and Progressor was 4(16%) and 8(42.1%) patients respectively.

Nephrotic Proteinuria and Oliguria were the dominant clinical features in Progressors, but macroscopic hematuria was the predominant feature found in Non Progressors.



	non progressor(n= 25)	progressor(n= 19)
macroscopic hematuria(28%vs21%)	7	4
oliguria(64% and 73.6%)	16	14
nephrotic proteinuria(16%vs 42.1%)	4	8

Body Mass Index:



Average Body Mass Index of our patients was 22.21 kg/m^2; Body Mass Index varied from 16 to 30.1 kg/m^2. Average Body Mass Index of Non Progressor group was 22.9 kg/m^2 and Average Body Mass Index of Progressor group was 21.18 kg/m^2. Body Mass Index of Non Progressors was found to be higher than Progressors (22.9±3.67 vs 21.19±3.20 kg/m^2).

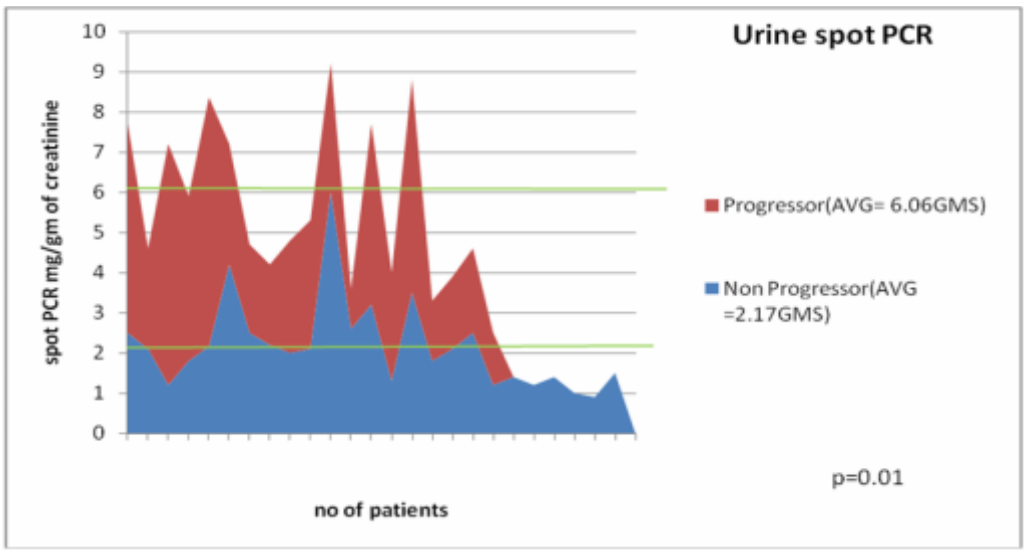
Statistical analysis of Body Mass Index using `paried t' test was not significant in predicting progression of disease (p=>0.05)

Urine spot PCR

Among the 44 patients 28 patients had frothy urine. Urine protein estimation varies from 2+ to 4+. Mean urine spot Protein Creatinine Ratio was 2.61 gm per gm of creatinine. Urine Spot Protein Creatinine Ratio of Non Progressor and Progressor was 2.16±1.13 and 6.06±1.59 gm of protein per gm

of Creatinine respectively. The Mean Urine Spot Protein Creatinine Ratio of Progressors was higher than Non Progressors.

Statistical analysis of Urine Spot Protein Creatinine Ratio by 'paired t' test was significant in predicting the progression of disease ($p<0.01$). Urine spot Protein Creatinine Ratio had a statistically significant correlation with Total MEST score by Pearson product moment coefficient ($p<0.01$).



Serum creatinine:

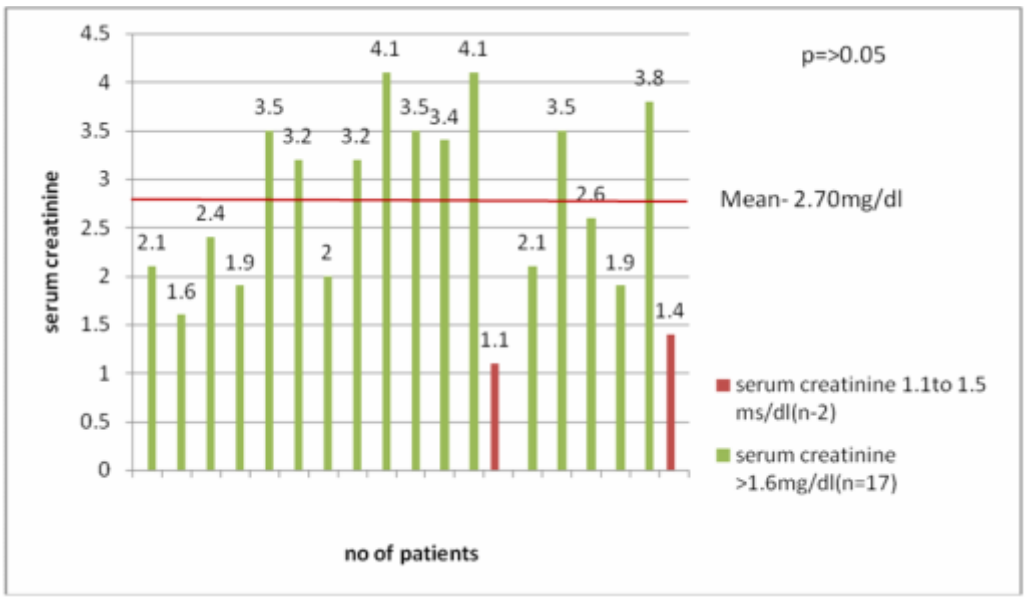
Serum creatinine	**Non Progresor (no of patients)**	**Progressor (no of patients)**
<1.0mg/dl	7	0
1.1 to 1.5 mg/dl	8	2
>1.6 mg/dl	10	17

Mean serum Creatinine of patients at the time of admission was 2.08mg/dl. Average serum Creatinine of Progressor (n=19) was 2.70 mgs/dl. Among the 19 patients 2 had Serum Creatinine of 1.1.to 1.5 mgs/ dl and rest of them had Serum Creatinine of >1.6mgs/dl.

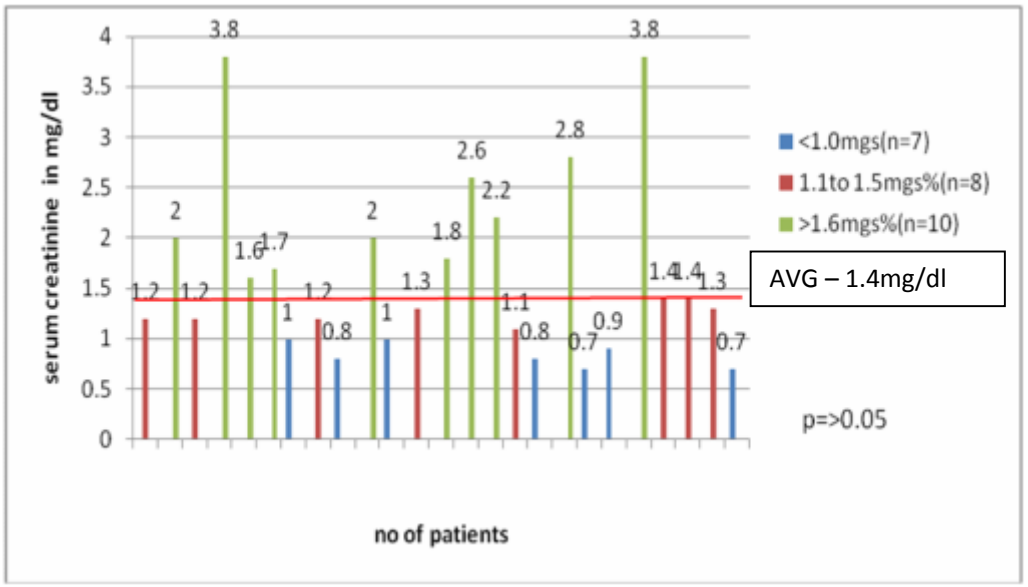
Among Non Progressors (n=25), 7 patients had Serum Creatinine of <1.0 mg/dl, 8 patients had Serum Creatinine of 1.1 to 1.5 mgs/dl and in rest of the patients (n=10) serum creatinine of >1.6mgs /dl was found at the time of presentation. Average Serum Creatinineof Non Progressor was 1.4mg/dl.

Statistical analysis using 'paired t' test was not significant in predicting disease progression with reference to Serum Creatinine (p=>0.05). Statistical analysis using 'paired t' test was not significant in predicting the high total MEST score with reference to Serum Creatinine (p=>0.05).

Serum Creatinine of Progressor:

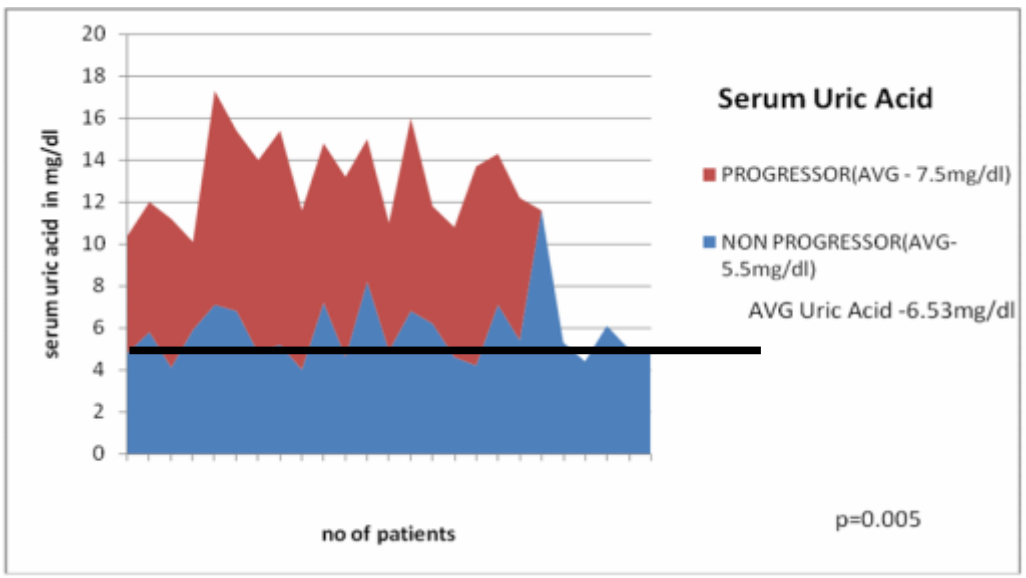


Serum creatinine of Nonprogressor:



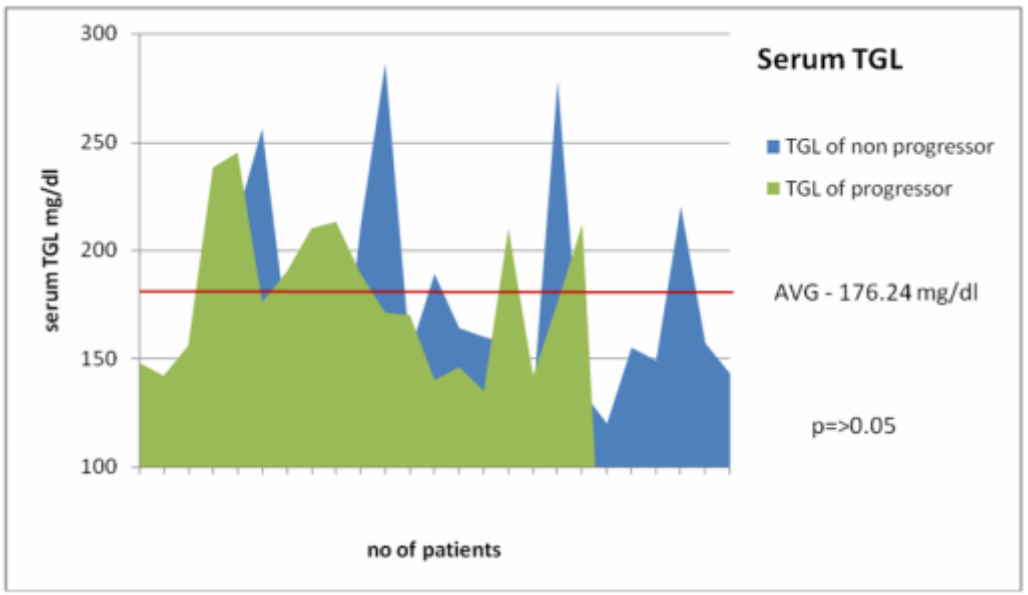
Serum uric acid:

Mean serum uric acid of study population was 6.53 mg/dl. Serum uric acid of Non Progressor was 5.8±1.65 mg/dl and Progressor was 7.5±1.69 mg/dl.



Statistical analysis using 'paired t' test was significantin predicting disease progression with reference to serum uric acid (p=0.005). In Pearson product moment coefficient correlation between serum uric acid and total MEST score was not statistically significant (p=>0.05). Serum uric acid is an individual predictor of disease progression.

Serum Triglyceride:



Mean serum Triglyceride 176.24 mgs/dl. Average serum Triglyceride of Progressor 179.5 mgs/dl (n=19). Average serum Triglyceride of Non Progressor was 176.8 mgs/dl (n=25). Statistical analysis using paired t test was not significant in predicting disease progression with reference to serum triglyceride (p=>0.05). Statistical analysis using Pearson product moment coefficient correlation, serum Triglyceride was not significant in predicting high total MEST score (p=>0.05).

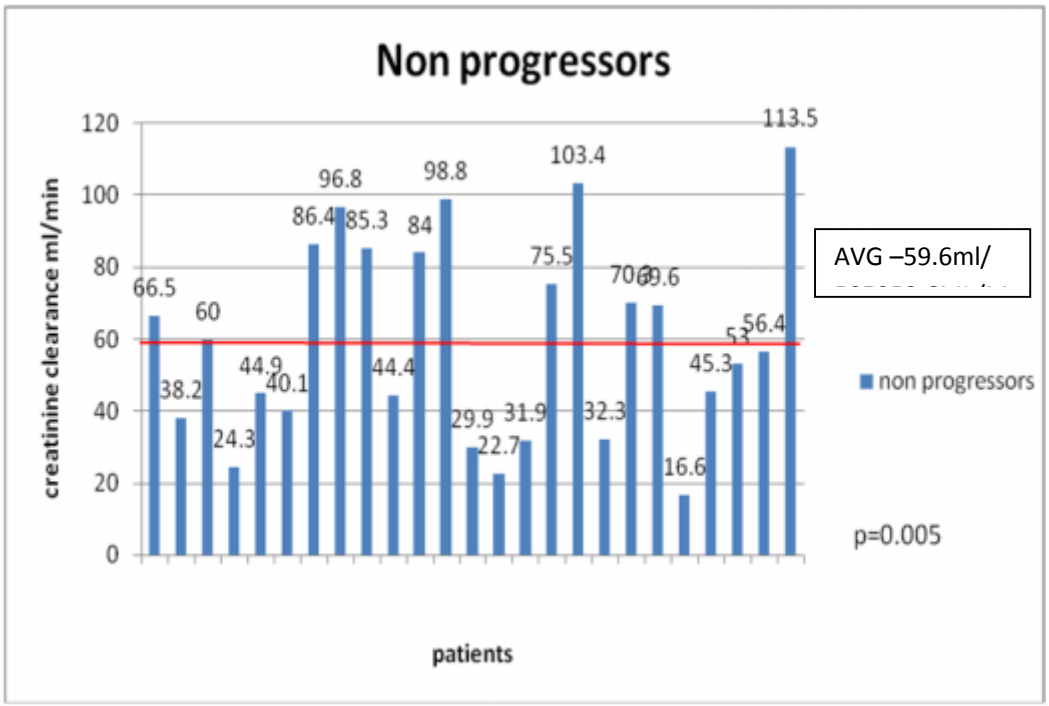
Creatinine clearance:

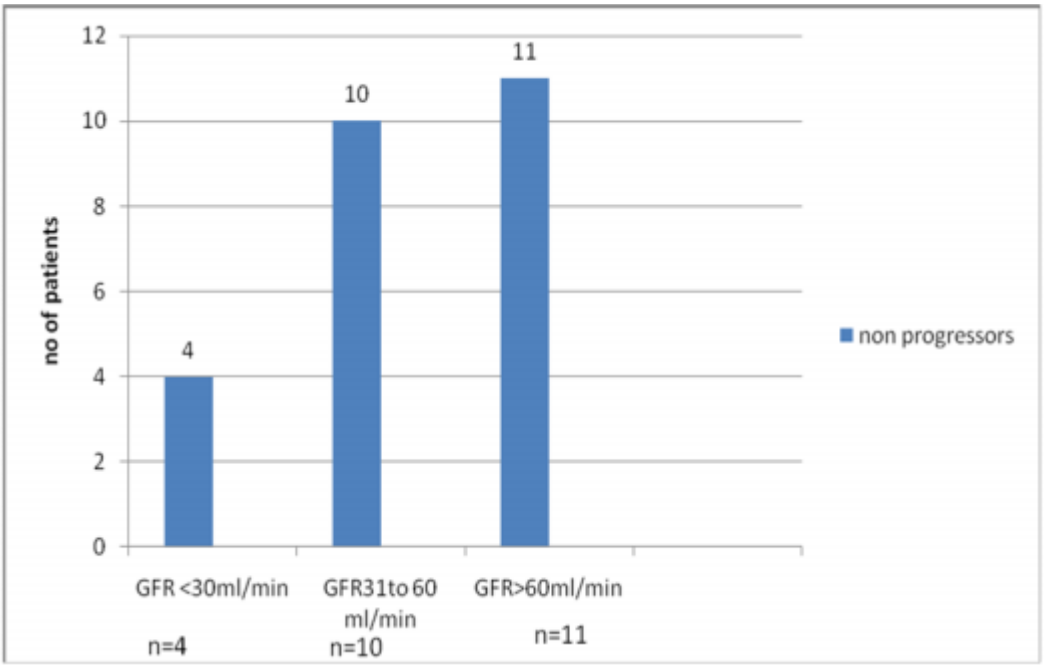
Mean Creatinine Clearance is 59.60 ml/min, with values varying from 14.3ml/min to 113.5ml/min. Average Creatinine Clearance of Non Progressors and Progressors was 59.6ml/min and 28.63ml/min respectively.

Glomerular Filtration Rate <30 ml/min was a feature in 4 (9.0%) and 12 (27.5%) patients of Non Progressor and Progressor group respectively.

Statistical analysis using 'paired t' test was significant in predicting the progression of disease with reference to Creatinine Clearance (p=0.005). Creatinine Clearance had a statistically significant correlation with Total MEST score in Pearson product moment coefficient correlation (p=0.01).

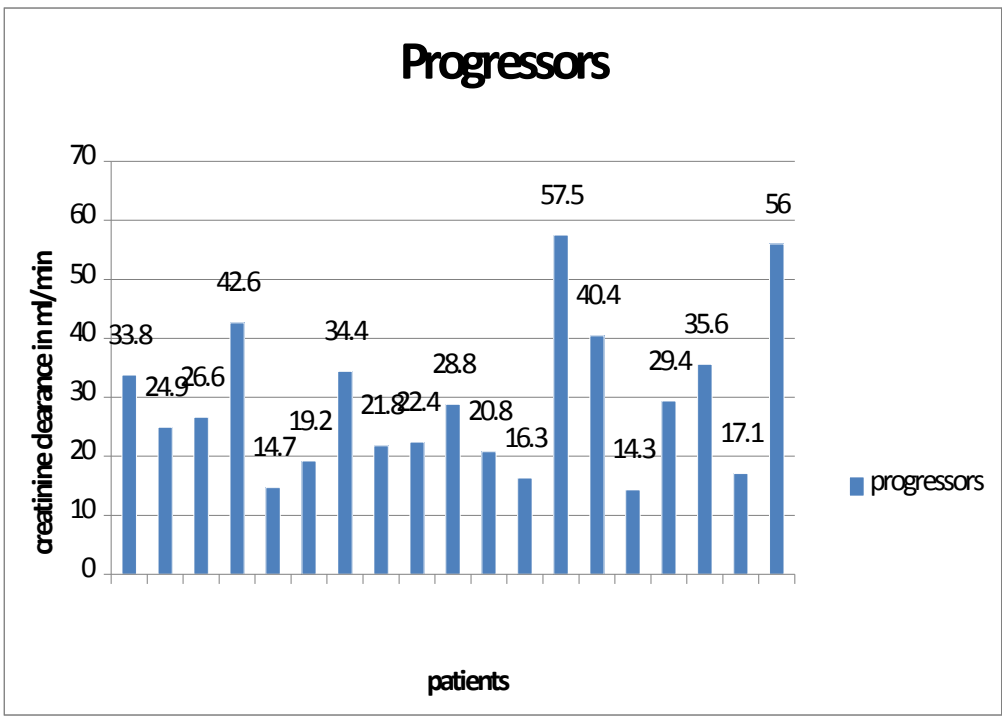
Creatinine Clearance of Non Progressors:

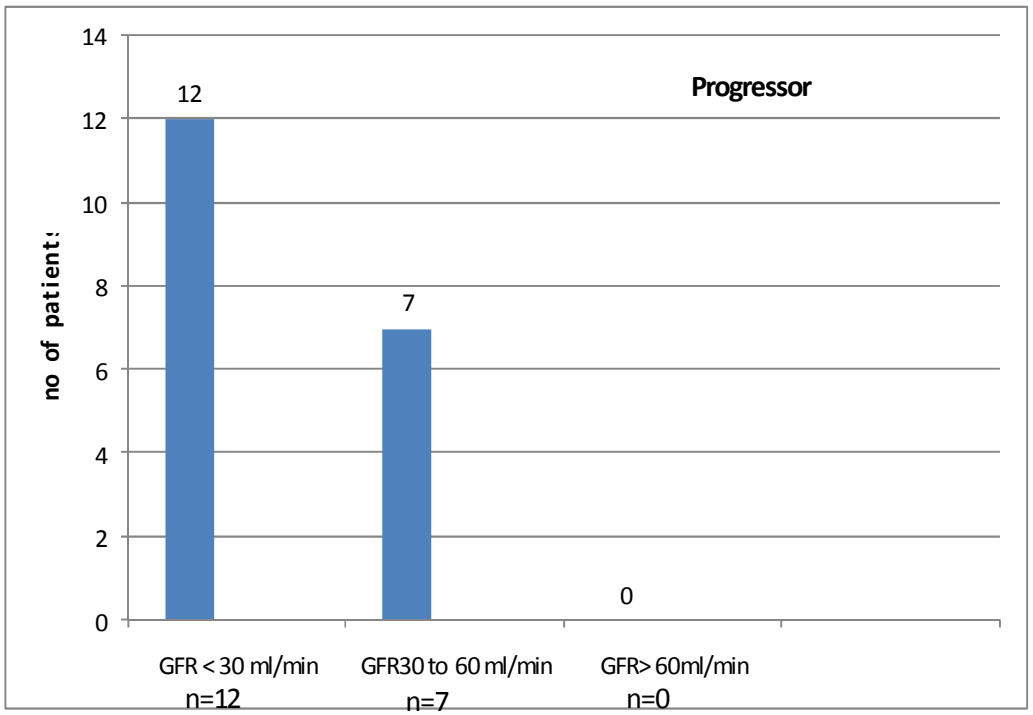




Creatinine Clearance of Progressors:

Average Creatinine Clearance of Progressors was 29.29 ml/min.





Baseline Creatinine Clearance is a statistically significant individual predictor of disease Outcome.

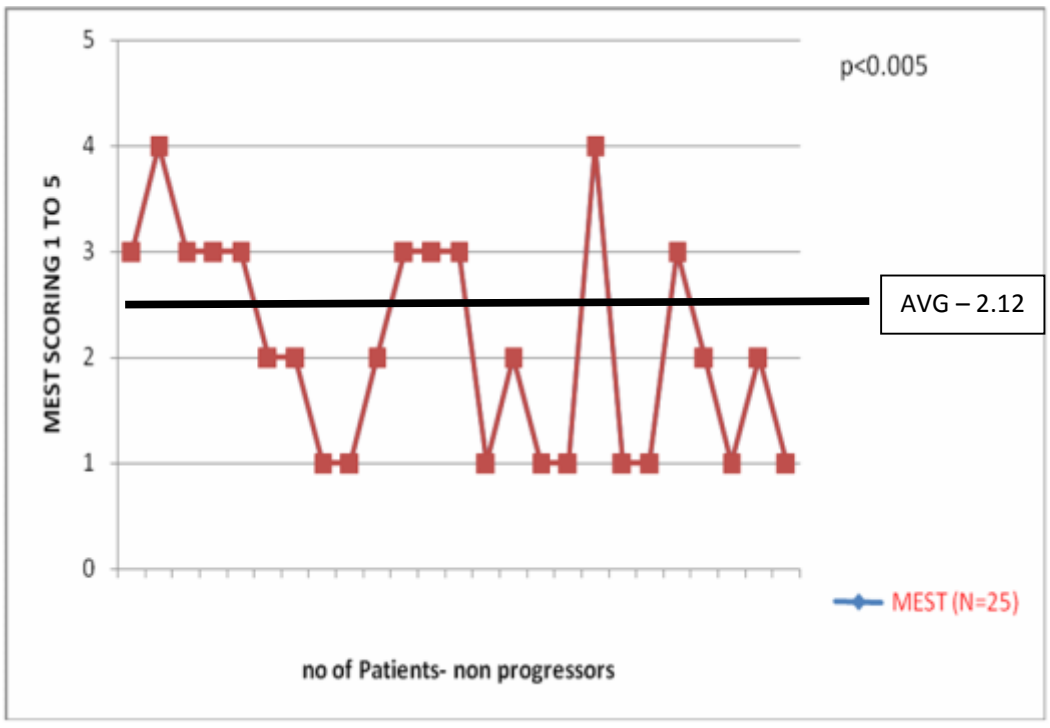
MEST scoring:

Total MEST score of cohort varied from 1 to 5, with mean of 2.64. 36% (9 patients) of Non Progressors had total MEST score of one. Total MEST score of 3 and 4 was found in 32% and 8 % of patients respectively in Non Progressors. In Progressors, 57.8 %(n=11) of patients had total MEST score of score 3 and score of 4 and 5 was found in 21% and 5.2% of patients respectively.

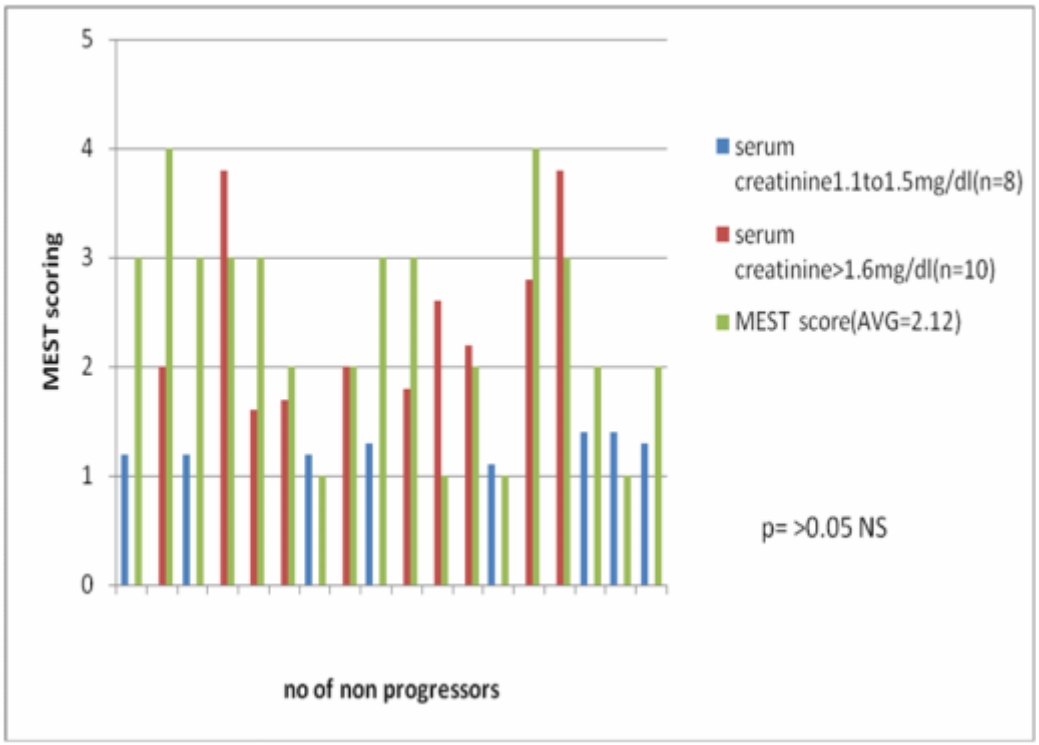
MEST score	1	2	3	4	5
Non Progressor	36% (n=9)	24% (n=2)	32% (n=8)	8% (n=6)	0
Progressor	0	15.8% (n=3)	57.8% (n=11)	21% (n=4)	5.3% (n=1)

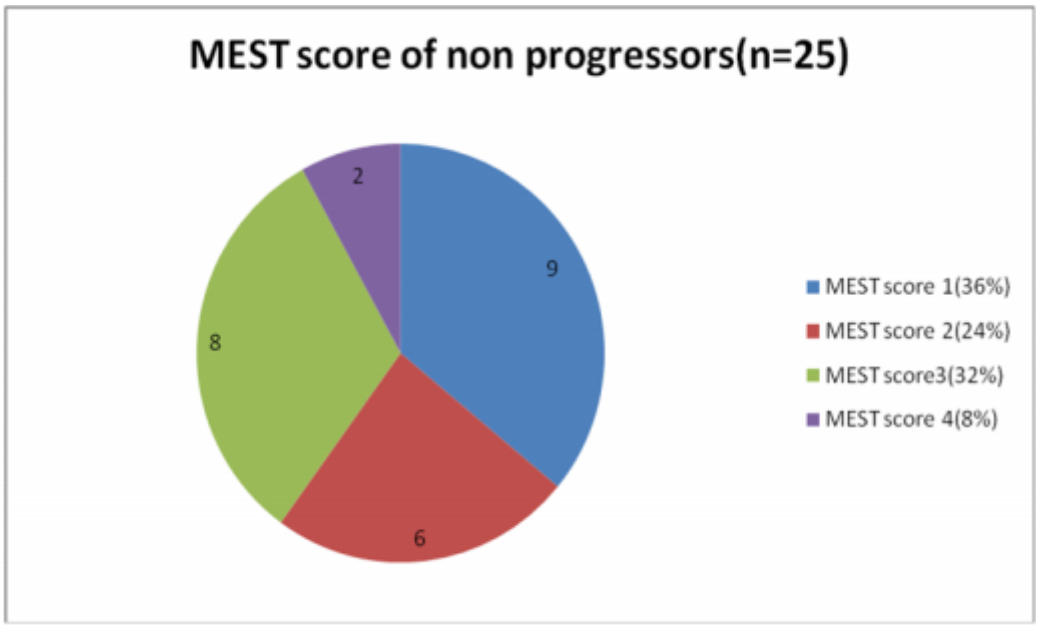
Mean total MEST score of Non Progressors and Progressors was 2.12 and 3.16 respectively. MEST score was higher in patients with Serum Creatinine >1 .6 mg/dl in both Non Progressor and Progressor group. High MEST score is a statistically significant individual predictor of Disease Outcome by paired t test (p=0.005).

MEST score of Non Progressor:

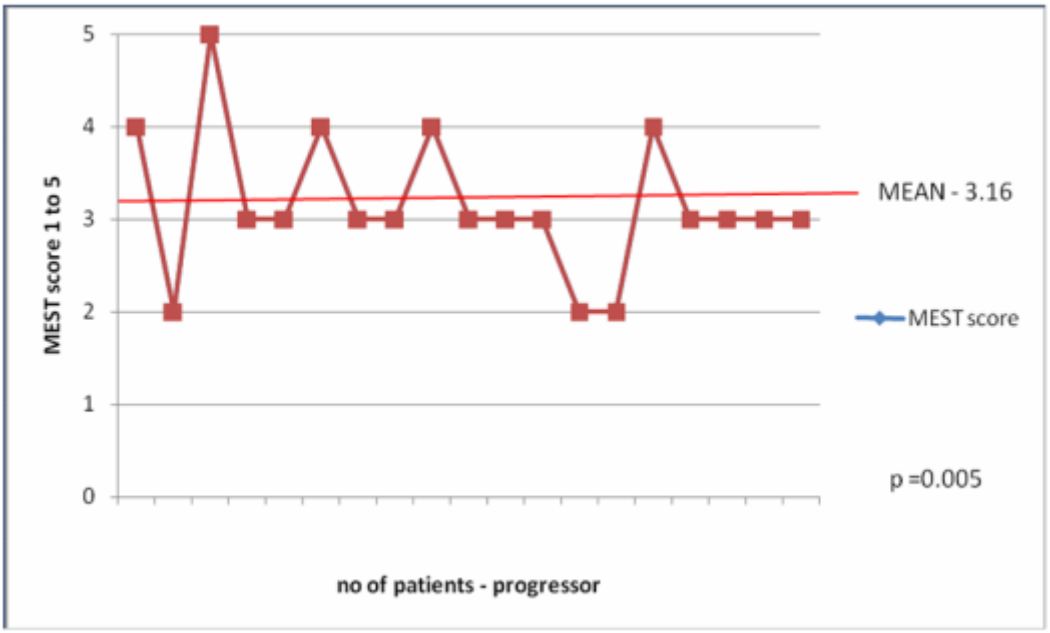


Serum Creatinine and MEST scoring in Non Progressor

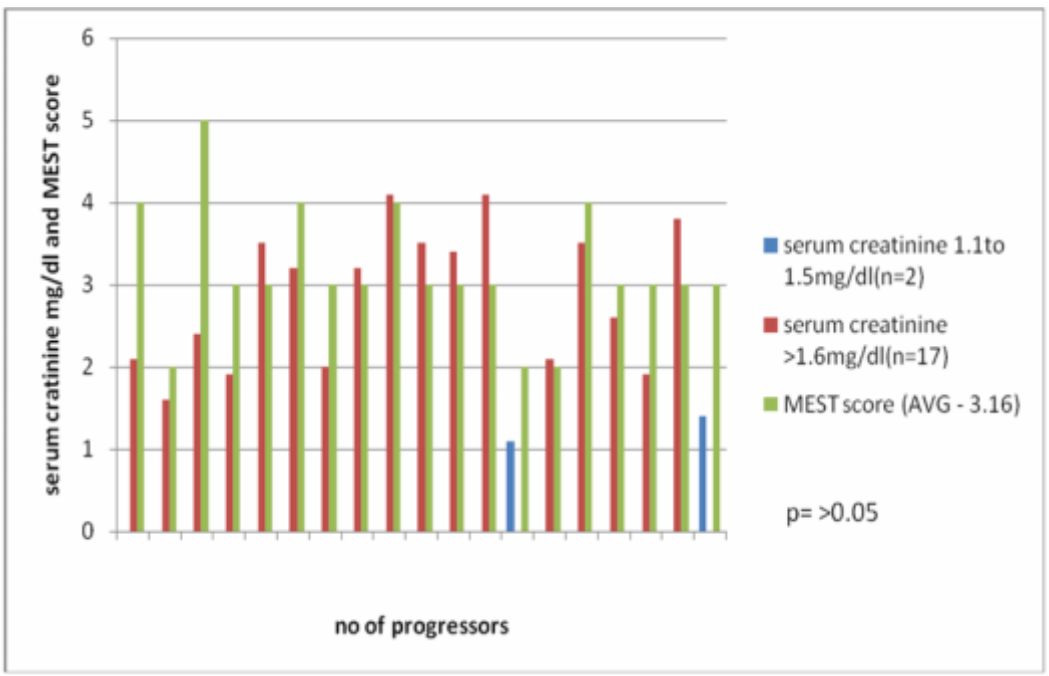


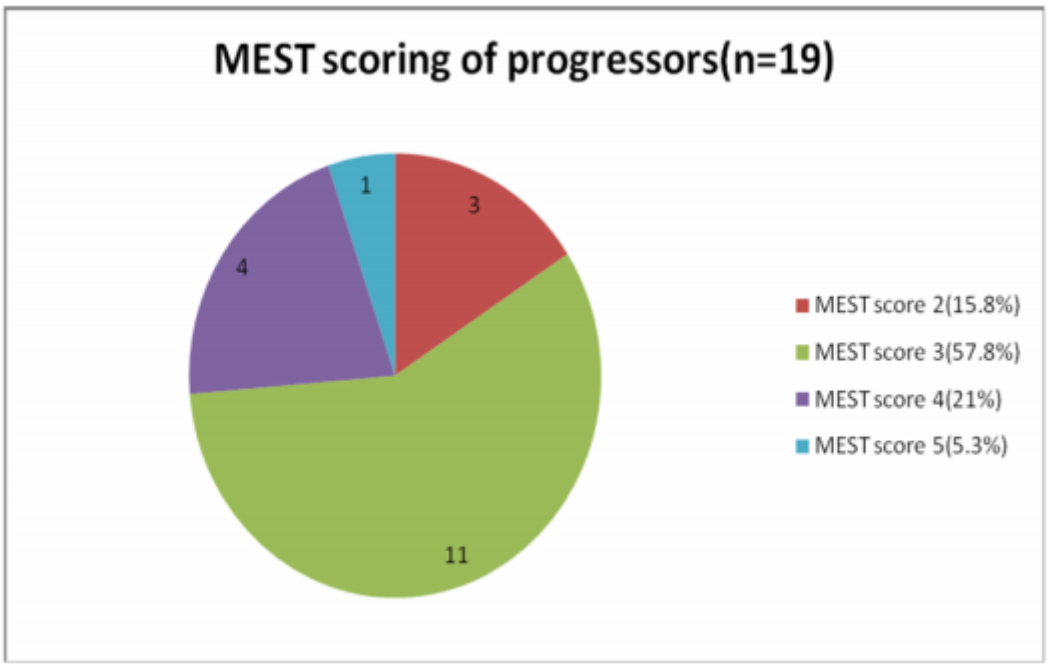


MEST scoring of Progressor:



Serum Creatinine and MEST score in Progressor:





Total MEST score of patients with serum creatinine of 1.1 to 1.5 mg/dl for Non Progressor and Progressor was 2.00± 0.93 and 2.50± 0.71 respectively. Total MEST score of patients with serum creatinine of >1.6 mg/dl for Non Progressor and Progressor was 2.70± 0.95 and 3.24±0.75 respectively.

In Paired t test analysis, no statistical significance was found between Total MEST score and serum creatinine in both non progressors and progressors (p=>0.05).

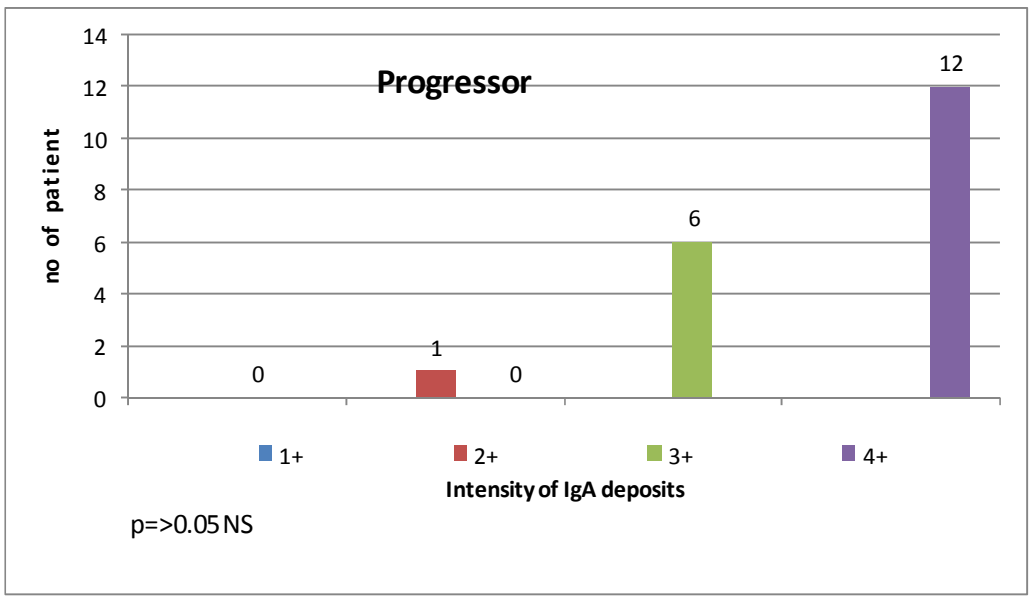
Pearson product moment coefficient correlation analysis was done between Mean Arterial Pressure, Urine spot Protein Creatinine Ratio, creatinine clearance, Serum Triglyceride and Serum uric acid with Total MEST score of Progresor and Non Progressor.

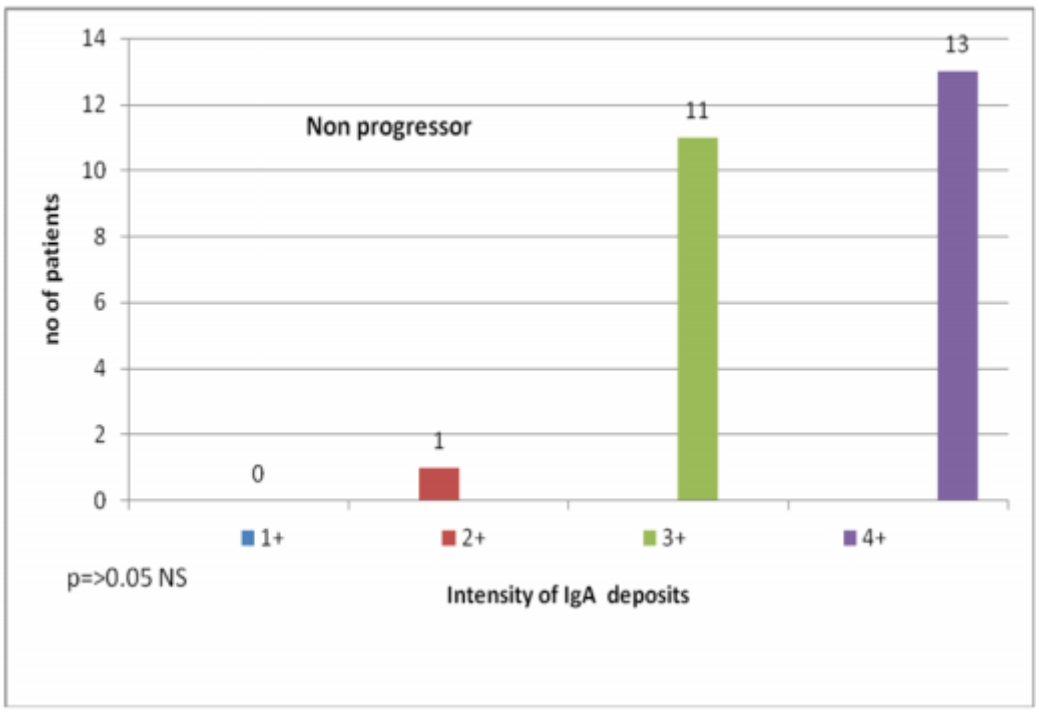
Statistical significant correlation was found between Urine spot Protein Creatinine Ratio and creatinine clearance with Total MEST score of Progressors (p=0.01). In Non Progressors, statistical significant correlation was found between Mean Arterial Pressure, Serum Triglyceride and Creatinine Clearance with Total MEST score (p=0.01).

Hence high urine spot Protein Creatinine Ratio and low Creatinine Clearance at the time of presentation predicts severe histopathological lesion (high Total MEST score) and poor outcome.

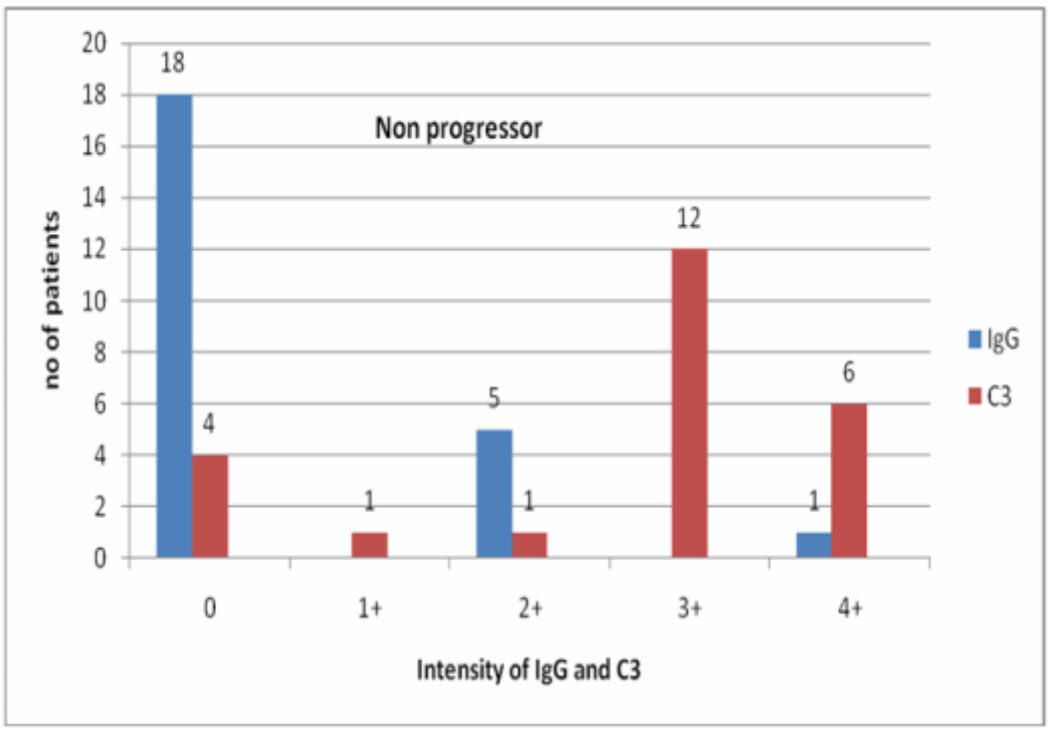
Intensity of IgA deposits:

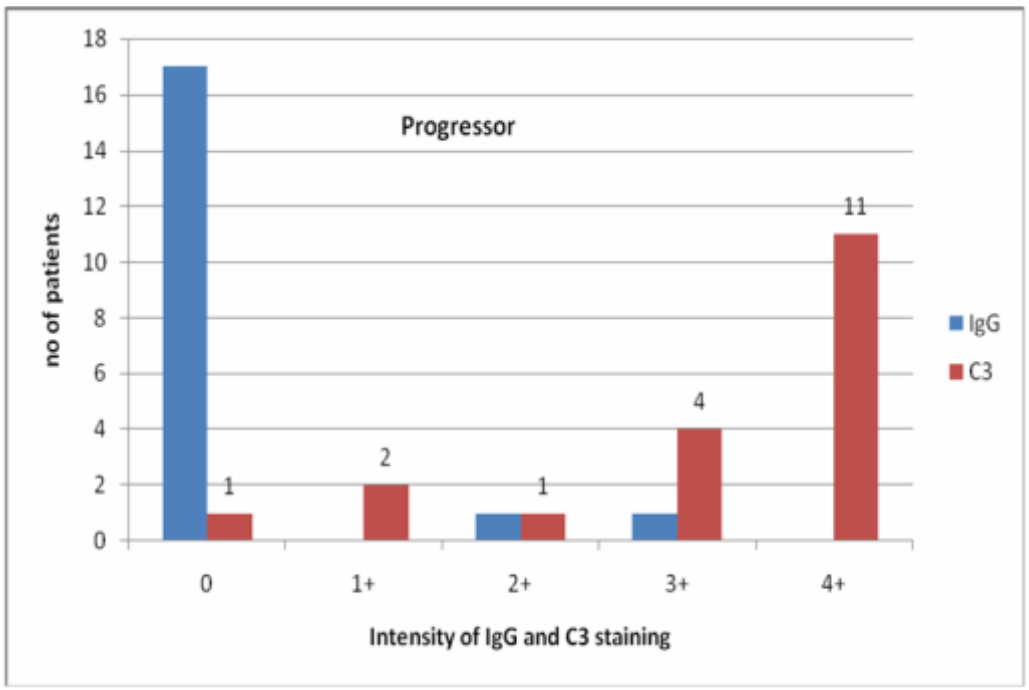
Intensity of IgA deposits varies from 2+ to 4+ in Immunofluorescence microscopy. 4 + was the intensity of IgA found in both Non Progressors and Progressors. Statistical analysis using paired t test was not significant in predicting the disease outcome with reference to IgA intensity (p=>0.05).





Codeposits in immunofluorescence microscopy:





Along with IgA, other immunoglobulins (IgG, IgM, C3, and C1Q) deposits were also found. Full house pattern (IgG, IgM, IgA) was found in 7 patients (6 – Non Progressors and 1 – Progressors),in all 7 patients C1q and ANA was negative.

Codeposits in immunofluorescence microscopy – Non Progressors:

C3 in the intensity of 3 + (12 patients) was the predominant co deposit found in non progressor and along with C3; IgG was also deposited with intensity of 2+in 5 patients.

Codeposits in immunofluorescence microscopy – Progressors

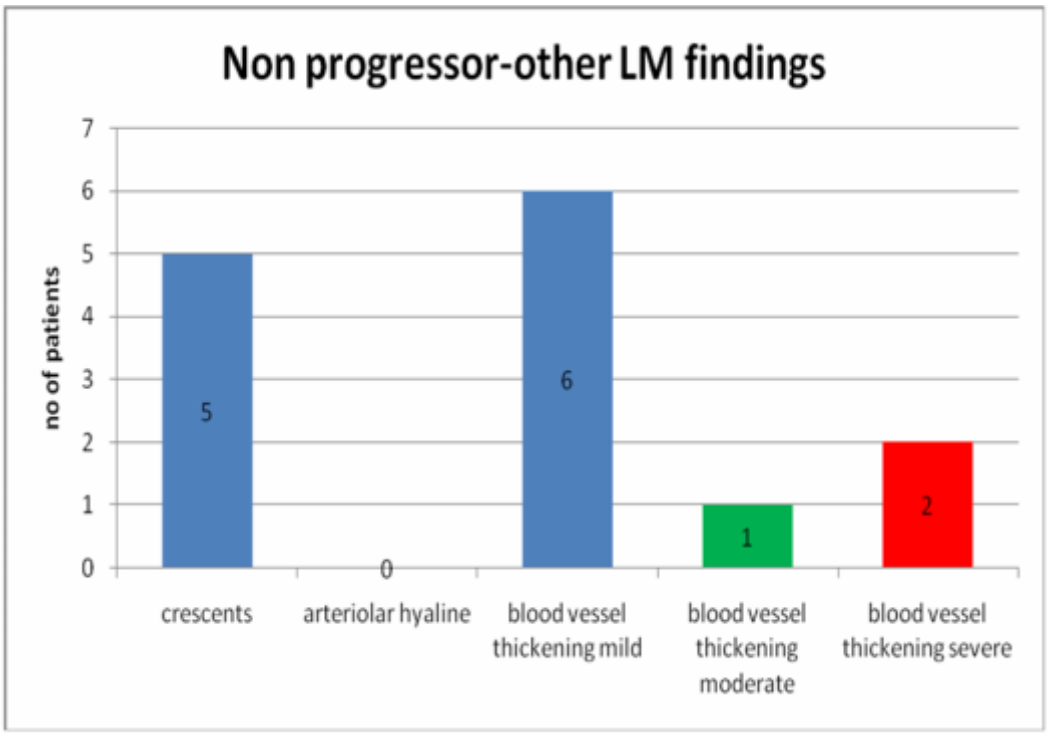
C3 in the intensity of 4 + was the predominant codeposit in immunofluorescence microscopy in Progressor (11 patients).

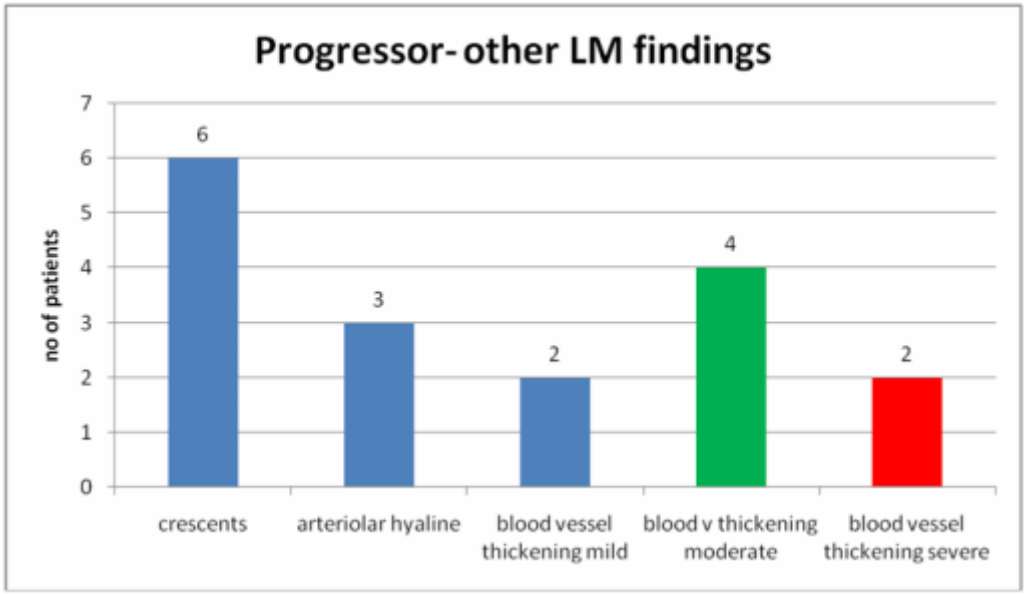
Other Histopathological features:

Cellular crescents, Arteriolar Hyaline and Blood Vessel Thickening were the other Histopathological features found in light microscopy.

In Non Progressor group, 5patients (20%) had partial Cellular Crescents. Blood Vessel Thickening was found in 9 patients (36%) with intensity varying from mild to severe. 2 patients (8%) had severe Blood Vessel thickening. None of the Non Progressor had Arteriolar Hyaline.

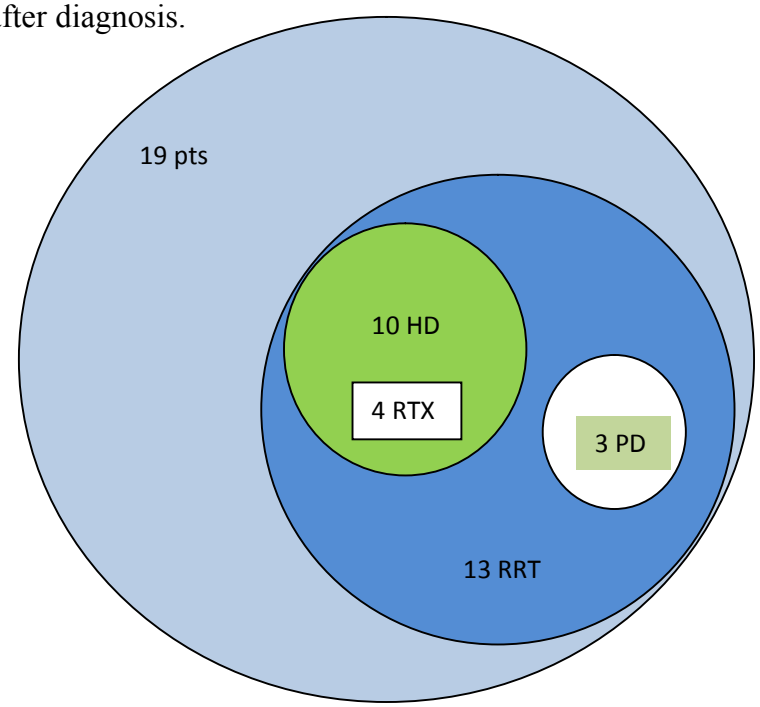
In the Progressor group Partial Cellular crescents was found in 6 patients (31.5%). 8 patients (42.1%) had Blood Vessel Thickening, among them 2 (10.5%) had Severe Blood Vessel thickening. Arteriolar Hyaline was found in 3 patients (15.7%).





Renal Replacement Therapy modalities in Progressors:

13 out of 19 patients were on Renal Replacement Therapy (Hemodialysis or Peritoneal Dialysis), 4 patients received live related renal allograft. Mean period to initiation of Renal Replacement Therapy was 5.2 months after diagnosis.



Multivariate analysis:

Correlation between Clinical, Histopathological and Renal Survival (outcome) was done using three models of multivariate analysis. ie Logistic Regression Analysis, Cox Regression Analysis and Kaplan Meier Series Analysis using SSPS 15 software. Age, Serum creatinine, Urine Spot Protein Creatinine Ratio, Creatinine Clearance, Individual and Total MEST score, Cellular Crescents, Arteriolar Hyaline, Blood Vessel Thickening and Time to Initiation of Renal Replacement Therapy were taken into account. End point for analysis was fixed as End Stage Renal Disease or Initiation of Renal Replacement Therapy. In Kaplan Meier series Correlation between T score and crescents with outcome (ESRD or initiation of Renal Replacement Therapy) was done.

Logistic Regression Analysis:

Predictability of the test was 68.2% with 95% confidence interval (CI). Correlation between clinical variables and pathological lesion with outcome was not statistically significant in predicting renal outcome.

Observed			**Predicted**		
			Dialysis		**Percentage Correct**
Step 0	**Dialysis**		**Absent**	**Present**	
		Absent	30	0	100.0
		Present	14	0	.0
	Overall Percentage				68.2

		B	S.E.	Wald	Df	Sig.	Exp(B)	95.0% C.I.for EXP(B)	
								Lower	Upper
Step 1(a)	AGE	-.007	.058	.015	1	.902	.993	.886	1.113
	CREATINE	.721	.772	.874	1	.350	2.057	.453	9.338
	URINE	.401	.443	.823	1	.364	1.494	.628	3.557
	CRCL	-.015	.059	.066	1	.798	.985	.878	1.105
	E	.818	1.988	.169	1	.681	2.266	.046	111.638
	S	-.063	1.849	.001	1	.973	.939	.025	35.155
	T	-1.142	1.657	.475	1	.491	.319	.012	8.206
	CRECENT	1.569	1.821	.742	1	.389	4.800	.135	170.310
	AH	.856	2.036	.177	1	.674	2.354	.043	127.380
	BV	.135	.673	.040	1	.841	1.144	.306	4.279
	RRT_TIME	.966	.395	5.987	1	.014	2.628	1.212	5.699
	Constant	-4.387	5.202	.711	1	.399	.012		

		B	S.E.	Wald	Df	Sig.	Exp(B)	95.0% C.I.for EXP(B)	
								Lower	Upper
Step 1(a)	AGE	-.022	.041	.271	1	.603	.979	.902	1.061
	CREATINE	.854	.714	1.430	1	.232	2.349	.579	9.529
	URINE	.399	.445	.804	1	.370	1.490	.623	3.564
	CRCL	-.007	.051	.019	1	.889	.993	.899	1.097
	CRECENT	1.482	1.754	.714	1	.398	4.403	.141	137.013
	AH	.980	1.961	.250	1	.617	2.664	.057	124.427
	BV	.146	.677	.046	1	.830	1.157	.307	4.363
	RRT_TIME	.916	.373	6.038	1	.014	2.500	1.204	5.190
	MEST_TOT	-.166	.826	.040	1	.841	.847	.168	4.280
	Constant	-4.809	4.563	1.111	1	.292	.008		

Cox Regression Analysis:

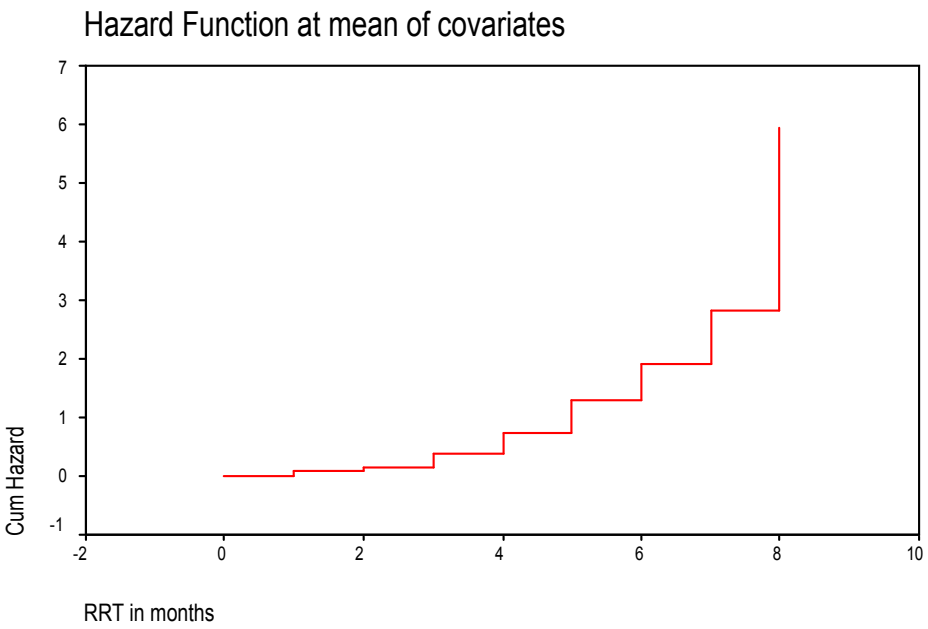
Overall predictability of the test was 93.2% with 95% of Confidence Interval (CI). Correlation between Clinical Variables and Pathological lesion

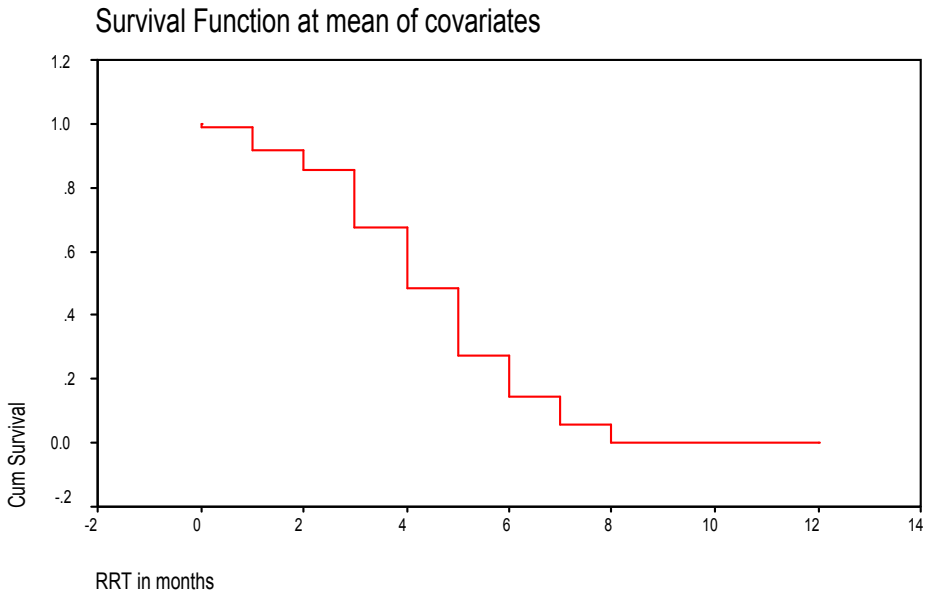
(MEST) with Outcome was not statistically significant in predicting renal outcome.

Observed			Predicted		
			Dialysis		Percentage Correct
Step 1	**Dialysis**		**Absent**	**Present**	
		Absent	28	2	93.3
		Present	1	13	92.9
	Overall Percentage				93.2

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
AGE	.054	.049	1.178	1	.278	1.055	.958	1.162
SEX	-.865	.892	.939	1	.332	.421	.073	2.421
CREATININE	.951	.666	2.040	1	.153	2.589	.702	9.550
URINE	.616	.411	2.243	1	.134	1.851	.827	4.143
Cr Cl	.049	.050	.951	1	.329	1.050	.952	1.158
M			.	0(a)	.			
E	1.370	1.829	.561	1	.454	3.934	.109	141.670
S	-.531	1.089	.238	1	.626	.588	.070	4.969
T	-.880	2.038	.187	1	.666	.415	.008	22.517
CRESCENT	2.136	1.878	1.294	1	.255	8.464	.213	335.631
AH	1.353	1.805	.562	1	.454	3.868	.113	132.953
BV	.494	.524	.888	1	.346	1.639	.586	4.582

		B	S.E.	Wald	Df	Sig.	Exp (B)	95.0% C.I.for EXP(B)	
								Lower	Upper
Step 1(a)	AGE	-.022	.041	.271	1	.603	.979	.902	1.061
	CREATININE	.854	.714	1.430	1	.232	2.349	.579	9.529
	URINE	.399	.445	.804	1	.370	1.490	.623	3.564
	Cr Cl	-.007	.051	.019	1	.889	.993	.899	1.097
	CRESCENT	1.482	1.754	.714	1	.398	4.403	.141	137.013
	AH	.980	1.961	.250	1	.617	2.664	.057	124.427
	BV	.146	.677	.046	1	.830	1.157	.307	4.363
	RRT_TIME	.916	.373	6.038	1	.014	2.500	1.204	5.190
	MEST_TOT	-.166	.826	.040	1	.841	.847	.168	4.280
	Constant	-4.809	4.563	1.111	1	.292	.008		





Kaplan Meier analysis:

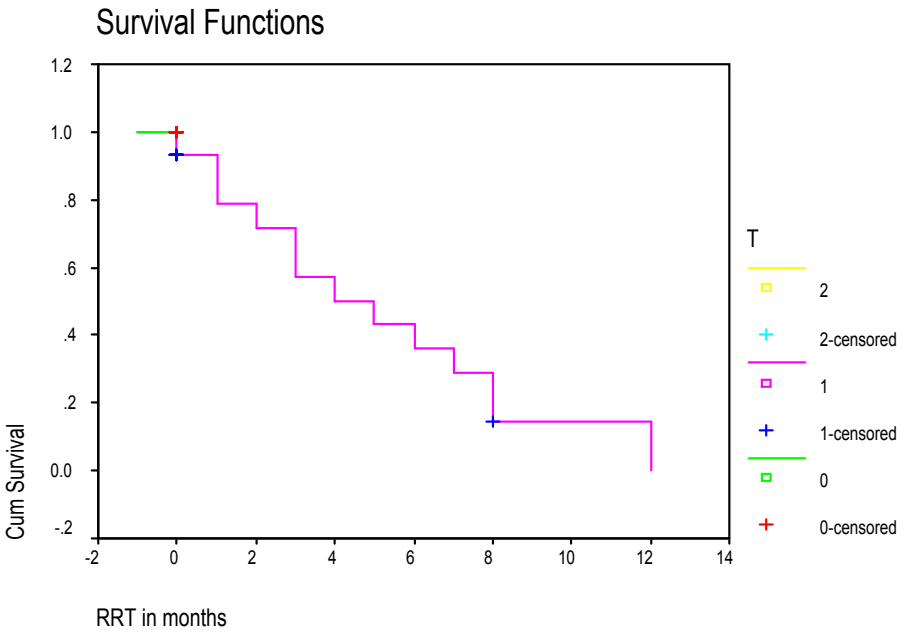
Predictability of the test was 68.18%. Correlation between T (Tubular) score and Cellular Crescents with Renal Outcome was statistically significant. These pathological lesions were Independent predictors of Renal Survival in Kaplan Meyer analysis. Clinical and other pathological features (MES – score, Arteriolar Hyaline and Blood vessel thickening) were not statistically significant.

Survival Analysis for RRT_TIME RRT in months

		Total Events	Number Censored	Number Censored	Percent
T	0	12	0	12	100.00
T	1	30	14	16	53.33
T	2	2	0	2	100.00
Overall		44	14	30	68.18

Test Statistics for Equality of Survival Distributions for T

	Statistic	df	Significance
Log Rank	.96	2	.6202
Breslow	.96	2	.6202
Tarone-Ware	.96	2	.6202



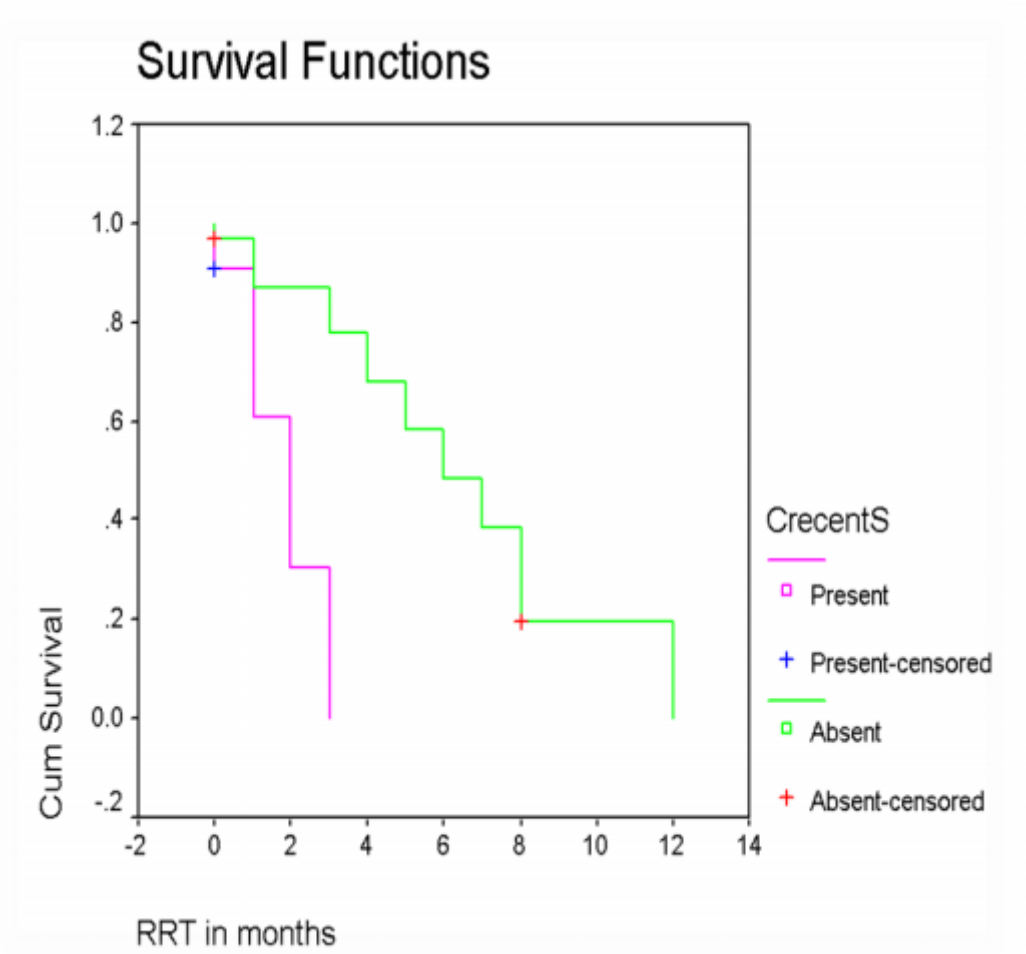
Kaplan meier analysis for crescents:

Survival Analysis for RRT_TIME RRT in months

		Total Events	Number Censored	Number Censored	Percent
Crescent	Absent	33	10	23	69.70
Crescent	Present	11	4	7	63.64
Overall		44	14	30	68.18

Test Statistics for Equality of Survival Distributions for CRESCENT

	Statistic	df	Significance
Log Rank	7.05	1	.0079
Breslow	2.65	1	.1035
Tarone-Ware	4.68	1	.0306



Discussion:

In our study, the incidence of IgA nephropathy is 16%. This result was comparable with a Retrospective study from Kerala, which showed an increasing trend of IgA nephropathy (15.52%) [18]. We also compared our study results with the previous reports, an incidence of 4.2% was reported from Tamil Nadu[11] in 1987, an incidence of 7.24% from New Delhi[12] in 1992, and an incidence of 10.37% from the Union Territory of Chandigarh[13] in 1995, and found an increasing trend of IgA nephropathy.

Radford MG etal[14] reported that, Primary IgA nephropathy occurs at any age, most commonly with clinical onset in the second and third decades of life. In discordant with this study report, our patients were predominantly belonging to 4th and 5thdecade and none of the patients had age of less than 15 years.

In similarity with the Ibels LS et al[15]study, males were predominant in our cohort. Hogg et al[64] (1994) observed 15 percent of the patients developed end stage renal disease in a mean follow up period of 4 yrs. In discordance with this study, 43.1% of our patients developed end stage renal disease in a mean follow up period of 17.2 months. Disease progressed more in younger age group between 15 to 30 years of age.

Mark Hass et al[50] sub classified IgA Nephropathy into subclass I(Minimal or No Mesangial Hypercellularity) subclass II (Focal and Segmental Glomerular Sclerosis without Mesangial Cellularity) subclass III(Focal

Proliferative Glomerulonephrits) subclass IV (Diffuse Proliferative Glomerulonephrits) and sub class V (>40% Global Glomerular Sclerosis and > 40% Tubular Atrophy).

Mark's clinicopathological analysis revealed that prognosis was better in sub class I and II, prognosis was intermediate in sub class III and prognosis was poor in sub class IV and V and additionally poor prognosis was found in the presence of Cellular Crescents, Fibro Cellular Crescents and Tubular Atrophy of > 20 %. Clinical findings like high Serum Creatinine, Nephrotic Proteinuria and Hypertension were also markers of poor prognosis. Mark et al[50]found that patients with Gross Hematuria had good prognosis. Apart from proteinuria and hypertension all other variables were not statistically significant.

In our study clinical factors like Proteinuria (Non Progressor and Progressor 2.16±1.13 and 6.06±1.59 mg per gm of creatinine p= 0.01), Serum Uric acid (Non Progressors and Progressor 5.8±1.65 mg/dl 7.5±1.69 mg/dl p= 0.005) and Creatinine Clearance (Non Progresors and Progressors 59.60±27.86 28.63±13.60 ml/min; p=0.005) were independent predictors of the outcome of the disease. When these findings were compared with the Clinicopathological correlation done by Hass, they were found to be concordant. Univariate Analysis with 'paired t' test confirms the statistical significance of these clinical variables.

In our study in addition to clinical factors, histological features like Cellular Crescents (20% Non Progressor vs 31.5% Progressor), Severe Blood Vessel Thickening (8 % Non Progressor vs 10.5% Progressor) and Arteriolar Hyaline were also associated with poor outcome (ESRD or initiation of RRT or doubling of serum creatinine).

In a large scale cohort study by Masashi Goto etal[65],a scoring system was proposed to estimate the ESRD risk within 10 yrs of onset of disease, using eight variables; these variables were 1.Male sex 2.Age less than 30 years 3.The presence of family history of chronic renal failure and chronic glomerulonephritis 4. Hypertension 5. Proteinuria and Mild Hematuria 6.Hypoalbuminaemia 7.LowGFR and 8.High Histological grade. This prognostic score accurately classified the patients by ESRD risk. Patients with estimated scores of 0–4.9, 5.0–19.9, 20.0–49.9 and 50.0–100% had an observed incidence of 1.7, 8.3, 36.7 and 85.5%, of progression to ESRD respectively. This prognostic score quantitatively estimates the ESRD risk during 10 year follow up and this serves as a useful prognostic tool in clinical practice.

In our study male sex, age <30 years, Nephrotic range Proteinuria, low Creatinine Clearance and Histological severity in the form of Tubular atrophy, Crescents, Severe Blood Vessel thickening and Arteriolar Hyaline were the variables associated with poor outcome (ERSD, doubling of serum creatinine or initiation of Renal Replacement Therapy). These results were in concordance with the results of a large scale cohort study by Masashi Goto[65].

In a single Center study of 146 patients done by Michael Walsh et al [66], three Histopathological parameters 1.Fibrosis of Interstitial area>25% 2.Sclerosis of Glomerular area> 40% and 3.Prescence of Crescents were found to be independent predictors of composite end point (doubling of serum creatinine, End Stage Renal Disease and Death). Clinical variables like significant Proteinuria (80%), high Serum Creatinine (38%) and blood pressure of >130/90 mm Hg (55%) were also predictors of poor prognosis.

Similarly in our study, patients with Nephrotic range Proteinuria had a statistically significant correlation with poor outcome. In addition, low Creatinine Clearance and high Serum Uric acid levels were also independent predictors of poor outcome.In discordant to this single center study by Michael Walsh et al[66], serum Creatinine was not a statistically significant predictor of disease outcome.

Comparing the Histopathological variables in our study, Tubular atrophy (T score>50 %) and Cellular crescents were independent predictors of disease progression (Using Kaplan Meier survival analysis). These results were similar to the study done by Michael Walsh el al.

A Working Group of the International IgA Nephropathy Network and the Renal Pathology Society introduced the Oxford MEST scoring system by analysis of 265 renal biopsy samples [60]. This analysis consists of four variables, Mesangial hypercellularity, Segmental sclerosis, Endocapillary proliferation and Tubular atrophy/ interstitial fibrosis.

In their series,15% of the patients were <18 yrs of age, Median follow up period was 5 yrs. Strong association was found between initial eGFR, MAP, proteinuria and poor renal outcome. Follow up Mean Arterial Pressure and proteinuria were also predictors of poor renal outcome. High MEST score were significantly associated with proteinuria. Segmental sclerosis, tubular atrophy and arterial disease were strongly associated with low eGFR and initial high MAP. Poor Renal outcome was significantly associated with mesangial hypercellularity, segmental sclerosis and tubular atrophy. These distinct pathological variables had prognostic value independent of all clinical and laboratory parameters. Endocapillary and extracapillary scores were not statistically significant in predicting adverse renal outcome. Immunosuppresive drugs were prescribed according to endocapillary or extracapliiary scores.

Oxford IgA Nephropathy classification was validated in North American cohort by Andrew M. Herzenberget al[62], using an independent cohort of 187 adults and children. Their clinical characters were comparable in age, eGFR, proteinuria and mean arterial pressure at time of biopsy with Oxford derivation cohort. Three of the four pathological variables as in Oxford cohort predicted the rapid decline in renal function. When compared to the Oxford cohort, North American cohort received more immununosuppresive drugs and anti hypertensives.

In similarity with OXFORD MEST scoring system and its North American cohort results, Clinical variables like Creatinine Clearance and

Nephrotic range Proteinuria were concordant in predicting therenal outcome.(Univariate analysis -paired t test) (p=0.005). Mean Arterial pressure was not a predictor of disease outcome in our study.

Correlation between Total MEST score and Renal outcome (ESRD/RRT) was statistically significant in univariate analysis (p=0.005). But Correlation between individual and total MEST score with renal outcome was not statistically significant in multivariate analysis (Logistic regression and Cox regression). T scores (Tubular) and crescents were found to be individual predictors of renal survival in Kaplan Meier survival analysis. Results of this multivariate analysis were discordant with OXFORD MEST scoring system and its North American validation.

As strict immunosuppressive protocol was not followed in our study, our treatment modalities are not comparable with other studies. All the 44 patients received Angiotensin Converting Enzyme inhibitors and Statins. Inj Methyl Prednisolone and oral Prednisolone was prescribed for patients with crescents for varied periods.

Conclusion:

In our study,

1. High Total MEST score at the time of presentation is an individual predictor of Disease Outcome.

2 High MEST score predicts Low baseline Creatinine clearance and Nephrotic Proteinuria.

3. Low baseline Creatinine Clearance, Nephrotic proteinuria and Serum Uric acid are individual predictors of disease progression.

4. Tubular atrophy (T score in MEST) and Partial Crescents individually predicts the Renal Survival.

5. MEST score is neither superior nor inferior in predicting the Renal Outcome when compared to Creatinine Clearance and Nephrotic proteinuria.

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